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PROTEIN SENSITIZATION IN THE PRODUCTION OF SKIN DISEASE*

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During the last decade there has grown up a voluminous literature on the subject of protein sensitization. Case after case has been reported in which it has been alleged that a skin disease of one form or another has been caused by the ingestion of some food substance. Laboratory workers have been equally busy with the clinicians and they, too, have done their part in adding to the literature.

In reviewing the papers on the various phases of protein sensitization the reader is soon impressed by the multiplicity of the substances accused of toxic action and the resulting anaphylactic shock and equally by the variety of the manifestations which these poisonous substances are alleged to produce. Moreover, the manifestations are not uniform in a given patient even in response to the same toxic stimulus but are various and varied. Neither do the symptoms seem to be constant, for not infrequently a food which was formerly not tolerated later may be innocuous for long intervals.

Prodromal symptoms are equally inconstant and fickle. The anaphylactic shock apparenty develops, often within a few minutes. In other cases it is seemingly delayed even for twenty-four hours or more. In some cases, notably in children, there are constitutional symptoms present in the interval between the poisoning and the reaction which, to the observing mother, indicates the imminence of anaphylactic shock. Nervousness, irritability, loss of appetite, sometimes diarrhea and sometimes fever are common prodromal signs, when such signs occur.

Moreover, many students assert that if the blood be examined at the time of the anaphylactic shock eosinophilia will be found for twenty-four hours or perhaps longer.

As already stated, the response in the skin to the influence of the toxemia is varied. Certain forms of skin manifestations, however, so predominate that in certain quarters they are accepted as satisfactory

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evidence per se of the existence of a state of anaphylaxis, i. e., that they are pathognomonic of anaphylatic shock. Preeminent among these are urticaria, angioneurotic edema and eczema.

Moreover, the dominant testimony of today places bronchial asthma and hay fever in the same category as manifestations of anaphylactic shock. Among many, the belief prevails that bronchial asthma and the skin diseases mentioned are merely variations of the same influence and may appear simultaneously or interchangeably. Therefore, in considering protein sensitization as a cause of skin disease, it is both necessary and illuminating to study the work done in bronchial asthma and hay fever.

One of the most striking facts in connection with the study of protein sensitization is the discovery that in many instances it is possible to detect the offending toxic substance by inoculation or vaccination of the skin. It has been found that when the protein which has sensitized the body is inoculated into the skin certain signs will follow. Moreover, the skin reaction is specific in the sense that the maximum skin reaction occurs only in response to the offending substance.

Even here, however, as will be shown later, all is not clear sailing for just as we have seen the clinical signs vary and even fail, so in response to the food inoculation test the skin does not always react or, if reacting, does so in a manner not explicable by the other evidence present.

It is evident from the foregoing that we are not dealing with a clear cut subject with well defined limits, but rather with a subject in which much work yet remains to be done. This thought has been well expressed by Loewit, whom I take the liberty of quoting.

> So great is the number of alleged shock producing substances and so manifold and changing is the picture drawn of the symptom complex attributed to anaphylaxis and so utterly unconfirmed and so lacking in character are the signs used in diagnosis that either suspicion is aroused of the great multiplicity and instability of the anaphylactic symptom complex or else we can only conclude that many of the processes laid at the door of anaphylaxis really possess only a superficial resemblance.[1]

None can deny that it is difficult to reconcile the changing and confusing claims of the anaphylactic enthusiast with our previous beliefs. The bond between the one time accepted theories and the newer theory of anaphylaxis is not yet complete. We seem to have but one course open to us, either to reject all that we once thought true and accept unreservedly the new theory or to agree with Loewit that the old truths remain unchanged and neither conflict with nor impair the newer facts now coming to light.

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1. Loewit: Ztschr. f. Immunitätsf. **27**:407, 1918.

We can perhaps make the situation clearer if we consider briefly, at this point, one or two clinical histories of typical cases of anaphylactic skin disease.

TYPICAL CASES

CASE 1.—First let me summarize Schloss' classic case. A boy, aged 8, had a pronounced idiosyncrasy to eggs, almonds and oats. The previous history is significant in its suggestion of contributing causes leading up to the subsequent anaphylactic developments. The little patient had suffered from seborrheic eczema, mild symptoms of rickets and repeated attacks of the respiratory tract. When 10 days old, the infant had a mild diarrhea for which he was given the white of an egg in barley water. No symptoms whatever followed its administration. When the boy received egg a second time he was 14 months old. Immediately he began to claw his mouth and tongue and the buccal tissues swelled to many times their normal size. Around the mouth typical urticarial wheals developed. Using von Pirquet's borer, Schloss was able to demonstrate the sensitiveness of the skin to egg white by the production of a typical wheal at the site of the inoculation. In the course of further study Schloss showed that the ovomucoid content of the egg white was the specific toxin.

A second case taken from my private records illustrates the multiple protein sensitization that so frequently occurs. It also exhibits the existence of a previous pathologic condition that suggests relationship to the later developing anaphylaxis. Finally, it illustrates the variability and instability of the cutaneous test reaction. The latter is most important as a majority of writers are inclined to accept the behavior of the cutaneous test as evidence of the progress of immunity. All these points will be considered later in greater detail.

CASE 2.—A shy, reticent boy of 7 years, while not appearing ill, lacked the activity and robustness of normal boys of like age. The history revealed that he had been well up to 3 years of age. At that time he had a light attack of measles. At first there was nothing noticeable about the attack and the disease followed the ordinary course. As recovery seemed about assured the boy suddenly had a convulsion and for some weeks was seriously ill with meningeal symptoms. When recovery finally came, the boy seemed to have lost all control over both the voluntary and involuntary nervous system. His mind was as clear and keen as ever, but, for example, when he tried to walk he could not make his legs move; when he tried to talk he could not indicate his desire in words although perfectly able to do so in signs. He had to learn all over again to walk and to talk.

From the point of view of the study of protein sensitization, the intolerance which had developed toward foods was most interesting. In Schloss' case just given there was a primary ingestion of a food substance without symptoms followed by sensitization and anaphylactic shock when the antigen, that is, the sensitizing food substance, was taken a second time. In this case, there was no such clear cut story. In his mother's words, the boy was converted from a perfectly normal child who could eat and digest everything given him to a child with a vasomotor system so instable and a digestion sensitized to so many foods that the possible diet was made extremely limited.

Cutaneous food tests were made with the following results: total number of substances tested, 59; total positive reactions, 26; total questionable reactions, 4; total negative tests, 29. The mother also reported her own clinical observations which, as she was more than ordinarily intelligent and observant, may be accepted without reserve. For example, she had learned that while the boy could not eat fresh bread he could eat toast. He could not eat the moist cereals. He could eat the dry cereals, shredded wheat, puffed rice, etc., i. e., those cooked by dry heat. In general, she had learned that foods baked or toasted, that is cooked by dry heat, were less liable to cause anaphylactic shock. Under the mother's careful guidance and by carefully cutting out those foodstuffs that gave a positive result to cutaneous tests, the boy has in the course of four years recovered much of his tolerance toward foods. He still cannot eat everything, but the number of toxic foods has been greatly reduced.

Up to within about a year the anaphylactic reaction manifested itself solely in the lungs. Following the ingestion of anaphylaxis-producing substances the child would have a most distressing asthma with noisy stridor and vomiting. He lost weight and strength during this time. For a year these asthmatic attacks have not been bad. For a year the explosion has manifested itself in the skin almost entirely, the lungs being often not at all or only slightly affected. After a period of irritability the skin breaks out in a generalized guttate eruption resembling both seborrheic eczema and psoriasis.

Preceding the attacks the boy was restless and apprehensive, was afraid to go to bed and would therefore sit up all night. The bowels would also become sluggish. An internist who had been consulted stated, after much study and experimentation, that he was convinced that the lower intestine and the large bowel were characteristically sluggish in functioning and in his opinion had much to do with the production of the anaphylactic state.

Repeated cutaneous food tests were made. During the early months of the case, while the anaphylactic state was at its height, the results were variable. A substance which one day gave a strongly positive reaction, three months later was often found to be negative only to become positive again after another longer or shorter interval. Likewise it was found that substances which when first tested were negative sometimes became, at a later time, positive and remained positive thereafter.

These complicated cases with their multiple figures and changing background at once invite the question, What does it all mean? We must seek the answer in the literature. It is, however, impossible to quote every reference or to consider every phase in detail. Both are too numerous. We can touch but lightly on the many phases of the subject and refer to but a few papers, choosing the most typical and best confirmed for quotation.

CAUSES OF PROTEIN SENSITIZATION

Heredity.—Our search naturally turns first to heredity as a cause of human sensitization. I could find no statistics bearing directly on the anaphylactic manifestations in the skin, but Cooke and Vander Veer[2]

2. Cooke and Vander Veer: J. Immunology, **1**:201, 1916.

give certain suggestive figures for that allied anaphylactic symptom, hay fever.

They estimate the frequency of human sensitization with clinical manifestations at probably less than 10 per cent. Granted that, as asserted, hay fever is the most frequent manifestation of all anaphylactic phenomena, the frequency with which the skin manifestations occur must be small.

Their figures, with regard to the frequency with which a negative or positive history of sensitization in one or both parents or in a collateral family branch was obtained, are interesting. In sixty-three apparently normal cases, there was a history of sensitization in the father or in the mother in 9.5 per cent. and a positive direct or collateral antecedent history in 14.5 per cent. Among 621 cases of sensitization, the antecedent direct or collateral history was negative in 260; positive in 205; positive on both sides in thirty-nine; that is, in 504 cases out of 621 there was some antecedent history in 48.4 per cent. About 19 per cent of the sensitized persons gave an entirely negative antecedent history. These figures they compare with the 14.5 per cent. positive antecedent histories obtained in normal persons, concluding therefrom that inheritance is a definite factor in sensitization.

Moreover, still speaking of hay fever, their further studies led them to the conclusion that the more complete the inheritance, the earlier the appearance of manifestations in the child. They also concluded that sensitized persons transmit to their offspring not their own specific sensitization, but an unusual capacity for developing bioplastic reactivites to any foreign protein.

These facts and figures are characteristic and are generally accepted by all writers on the subject.

Remembering that hay fever is accepted as the great exponent of anaphylactic manifestations and bearing in mind Cooke and Vander Veer's conclusions as to the transmissibility of protein sensitization, the student will find food for thought in contemplating and comparing Schreier's definition of arthritism or the arthritic diathesis. Schreiber [3] says: "Certain infants are thus born with a 'vice of nutrition' which will manifest itself in them through a specific (individual) reaction to various pathologic agents and will also render them vulnerable to conditions which do not affect the normal organism."

Gastro-Intestinal Diseases and Protein Sensitization.—Enough has already been said to justify a hasty review of current opinion concerning the possible relationship of gastro-intestinal conditions and protein sensitization. Leri [4] maintains that the anaphylactic state and the diath-

3. Schreiber: Arch. de med. des enfants **15,** No. 6, 1912.
4. Leri: Ann. de méd. et chir. **16,** No. 22, 1912.

eses possess too many characteristics in common for their similarity to be no more than apparent. Lesné and Dreyfus [5] speak of alimentary anaphylaxis, meaning a process of protein sensitization arising in the alimentary tract. Johnston [6] asserts that "anaphylaxis in the human being commonly expends its force not on the respiratory apparatus but on the gastro-intestinal tract, as is amply proved by cases of serum disease. After all, it matters very little whether indigestion is primary or secondary. It claims attention in either event." Johnston found that hyperacidity occurred more frequently than any other form of digestive disturbance. Sensitization, he says, occurs during the period of frank indigestion.

Combe [7] supplements Johnston's views. He says that when the albumins, and especially the fats, in the body are destroyed too rapidly the organism becomes poisoned, a state of acetonemia or acid intoxication resulting. According to Combe, any inflammatory or atrophic changes in the intestinal mucosa favor intestinal putrefaction and hence intestinal toxemias. The same is also true of intestinal stasis.

Dr. V. C. Vaughan [8] furnishes a further hint as to the possible rôle played by the digestive functions in the production of protein sensitization. Writing of the relation of anaphylaxis to immunity and disease, Vaughan says that in producing a state of anaphylaxis or immunity by the injection of certain proteins, the digestive secretions are modified according to the protein used, so that each protein has a specific ferment which acts on no other protein. This process he calls sensitization and states that it may be transmitted to the offspring.

The Liver and Toxemia.—Manwaring [9] found that the liver played an important rôle in general toxemia. In dogs, cutting out the liver from the general circulation also cut out the anaphylactic shock. The reaction, he concludes, occurs chiefly in the liver. Rumpf [10] verified Manwaring's observations by experiments on guinea-pigs, from which he too concluded that the chief effects of the anaphylactic process take place in the liver epithelium.

Combe says that the body has three lines of defense against intoxication and autointoxication, the first being the intestinal mucous membrane, the second the liver and the third the ductless glands. Anything that interferes with the functioning of the liver exposes the organism to invasion by toxins. It is not for nothing, Combe says, that all the blood

5. Lesné and Dreyfus: Ann. de méd. et chir. **16,** No. 22, 1912.
6. Johnston: J. Cutan. Dis. **30**:96, 1912.
7. Combe: Intestinal Autointoxication, New York, Rebman, 1910.
8. Vaughan, V. C.: Am. J. Med. Sc. **145**:161, 1913.
9. Manwaring: Ztschr. f. Immunitätsf. **8**:1, 1911.
10. Rumpf: Ztschr. f. Immunitätsf. **27**: 1918.

from the intestine must flow through the liver where the liver cells rob it of its poisons. In this, Combe verifies Rumpf and Manwaring.

Ductless Glands and Toxemia.—Janney and Isaacson [11] furnish corroborative testimony as to the value of the ductless glands in the defense of the body from their study of thyroidectomy and thyroid diseases on protein metabolites. Stated briefly, they found that thyroid disease favors protein catabolism thereby linking the thyroid to anaphylactic disease in which, according to the majority of writers, protein catabolism is a prominent feature.

Fordyce writes that owing to the frequent association of urticaria with hay fever and asthma, conditions commonly found in hyperthyroidism, the glands of internal secretion so influence the vessel tone by their products that they form an important factor in the production of anapyhlaxis.

Johnston maintains that the study of a case of urine anaphylaxis in any skin disease is not complete which does not determine the percentage of these bodies (the nitrogen compounds) in the urine. In his experience the most frequent change was a decrease of urea and a corresponding increase in the rest nitrogen fractions, and that when it was marked, symptoms could be looked for.

Eosinophilia.—Among other points most commonly emphasized in the diagnosis of anaphylaxis is the occurrence of eosinophilia. Some writers, indeed, lay so much stress on this phenomenon as to create the impression that they believe it a pathognomonic symptom. Others, perhaps the majority, consider it of lesser importance.

Weinberg and Sequin [13] state that in the anaphylactic process an eosinophilia appears in from one to three days after reinfection of the antigen. They explain the appearance by the hypothesis of a direct irritation of the hemopoietic system by the antigen. Rackemann [14] adopts Staubli's theory to explain that a foreign protein acts as an eosinotactic substance.

These quotations sufficiently illustrate the general trend of opinion.

In contrast to this use of an eosinophilia as a symptom of anaphylaxis is the similar use of eosinophilia as a characteristic of the arthritic diathesis. For example, Schreiber, writing of the diatheses of infancy, quotes Dr. Finkelstein's assistant, Rosenstern, as having brought out a new point in connection with infantile arthritism. Rosenstern says, "Having practiced the examination of the blood of infants suffering from troubles in the skin or mucous membranes of the arthritic series

11. Janney and Isaacson: Arch. Int. Med. **22**:160 (Aug.) 1918.
12. Fordyce: J. Cutan. Dis. **30**:128, 1912.
13. Weinberg and Sequin: Compt. rend. Soc. de biol. **76**.
14. Rackemann: Arch. Int. Med. **22**:517 (Oct.) 1918.

(eczema, prurigo, asthma, various catarrhs, etc.), I was able to demonstrate an eosinophilia, sometimes reaching 20 per cent." Schreiber therefore concludes that an eosinophilia is common to all diathetic manifestations.

Combe considers an eosinophilia a manifestation confidently to be expected in intoxications and autointoxications.

The questions arise, What value shall we attach to eosinophilia? On eosinophilia as a basis, what relationship shall we assign to protein sensitization and the diatheses and intoxications?

If we turn to a consideration of the prevailing theories of anaphylaxis to help us to a decision we are met with disappointment. In spite of the just expectation that the immense amount of work and research, of which the large and rich literature on the subject is evidence, would yield some definite opinion or standard, we find controversy raging in this field also.

THEORIES OF ANAPHYLAXIS

Humoral Theory.—There are two theories in existence today, the humoral and the cellular. Both have their advocates and their opponents. Friedberger[15] may be taken as a representative of the humoral theory. His theory teaches that the process which results in sensitizing the organisms takes place in the blood. The argument runs that if egg albumin is injected into an animal it causes antibodies to be formed in the injected animal's blood. If the antigen (egg-albumin) is reinjected into the animal thus prepared, a reaction takes place in the blood between the reinjected antigen and the antibodies prepared by the previous injection of the antigen. The presence of complement is, however, necessary. Further, as a result of this reaction between antigen, antibody and complement, the albumin molecule is broken down and a toxic product is formed known as anaphylatoxin. It will be readily seen that this theory agrees closely with the old views of the toxemias.

More recently a second theory has sprung up, and is seemingly growing steadily in favor, which opposes the humoral theory on the ground that the mere meeting of antigen and antibody in a complement containing medium does not adequately explain the symptomatology of anaphylactic shock, particularly the latent period of passive transmission.

According to Weil,[16] the humoral theory is committed to the belief that the circulating antibody may exercise either a protective or an injurious function whereas the cellular theory is strictly correlated with the view that the circulating antibody is invariably protective and the cellular antibody is invariably the agent of anaphylactic symptoms

15. Friedberger: Ztschr. f. Immunitätsf. **4**:218, 1910.
16. Weil: J. Immunol. **1**:1, 19, 35, 47, 1916.

Cellular Theory.—Weil had previously stated that as a result of his study he had come to the conclusion that antigen and antibody could not coexist in the same field without union.

All writers agree that time is needed to produce the conditions necessary to anaphylactic shock. As Vaughan [17] expresses it: "If a reinjection of protein is made before a large amount of specific ferment is formed, no anaphylactic shock results. Anaphylactic shock is not to be feared if less than twelve days intervene between the first and second injections. Goodall [18] says that on an average a week or more is required for "incubation" between the primary sensitizating dose and the second activating dose.

Fordyce described the process of anaphylaxis as follows:

A foreign protein introduced into the organism causes an increase of antibodies for this protein. If after a so-called incubation period a second dose is given, the protein will be so rapidly disintegrated by the antibodies that toxic products are set free which give rise to the clinical phenomena. A further disintegration renders them harmless and the attack subsides.

Barduzzi says toxic substances that are formed in the blood or organic fluids act on the nerve cells. Urticaria is due to anaphylaxis. The symptoms are due to an irritation of the endothelium.

Rumpf found that the anaphylactic state persisted when the blood of a sensitized guinea-pig was removed and the blood of a normal animal substituted. Had the active agent of the anaphylactic phenomena resided in the blood desensitization should have ensued. Such was not the case, thereby proving that the reaction was cellular.

In brief, we may summarize the cellular theory, taking the facts from heterogeneous sources. A foreign protein is introduced into the organism. No symptoms follow. Antibodies are formed for the injected protein which are absorbed, anchored by the cells. Until enough antibodies have accumulated and have been anchored in the cells there will be no response to injections of the protein. Finally, however, the introduction of even a small dose of the sensitizing protein causes an explosion. "The reaction is an expression of the alteration of cellular equilibrium which results when external antigen is brought into contact with the cellular antibody" (Weil).

This theory is held by the proponents to answer all the objections raised against the humoral theory. It particularly explains the latent period of sensitization which the humoral theory could not. It is the period during which the process is gathering headway, when the cells are capturing and anchoring the antibodies as they are formed.

17. Vaughan: Am. J. Med. Sc. **145**:161, 1913.
18. Goodall: Brit. J. Child. Dis. **9**:433, 1912.

The antibodies are so essential to the process of anaphylaxis that, naturally, much work has been expended in trying to demonstrate their presence.

Von Fenyvessy and Freund's [19] report of their studies is to the effect that the presence of antibodies in the circulation is not necessary to anaphylactic shock. As has already been shown in discussing other topics, this agrees with current opinion.

Perhaps one reason for lack of success in finding circulating antibodies lies in the results indicated by Hilda Hempl's [20] studies that in general a foreign serum disappears more quickly from the blood of an animal sensitized to that serum than from that of a normal animal, and that it disappears more quickly from the blood of a highly reacting animal than from that of a slightly reacting animal.

THE CUTANEOUS FOOD TEST

Schloss was among the first to demonstrate the possibilities of the cutaneous food test in cases of protein sensitization. Since that time the test has been developed widely both in use and in technic until today the average practitioner is as inclined to accept unquestioningly the apparent teachings of its results as he is to accept the results of the Wassermann test in syphilis. A brief study of the literature suggests that the circumstances surrounding the two are similar. Both tests lack full understanding. Both have their vagaries acting as they should not on the face of the evidence. Both are stronger on their positive than on their negative sides.

A few quotations will illustrate wherein the cutaneous food test is strong and wherein it is weak.

> The cutaneous food test may be taken as an index that the body cells have been brought into contact with a certain protein and that in addition to the production of the anaphylactic state antibodies of a protective and curative nature are produced. Cutaneous anaphylaxis cannot be accepted as a direct or reliable evidence of actual immunity any more than the agglutinins in the same capacity.[21]

> There is no experimental support for the theory that allergic skin reaction may be taken as an index to resistance and immunity insofar as it is possible to determine the presence of antibodies in vitro.[22]

Walker, writing on bronchial asthma, says that since many patients were sensitive to proteins of foods not eaten every day as well as to the foods eaten regularly, it is hard to say what part the less frequently

19. Von Fenyvessy and Freund, J.: Ztsch. f. Immunitätsf. **22**:199, 1914.
20. Hempl: J. Immunol. **2**:141, 1917.
21. Kolmer and Berge: J. Immunology **1**:409, 1916.
22. Kolmer: J. Immunol. **3**:10, 1918.

eaten foods play. Furthermore, he continues, the fact that many of these patients have eczema as well as asthma complicates the interpretation of the positive skin test but does not detract from the value of the test. Speaking of the skin test as an index of desensitization, he says that usually the positiveness of the skin test decreases as the amount of protein in the treatment increases, provided the increase is slow and gradual. If the protein treatment is increased too rapidly, the skin test and desensitization cannot keep pace, so that eventually anaphylactic shock may result from the treatment.

Walker implies, in explaining the failure of the skin test in two patients, that a hyperirritable skin may give unjustified results.

That the skin test is not always positive when it may clinically be expected to be is shown by Rackemann's figures. Skin tests were done in 127 cases. One or more tests were positive in seventy-four cases (50 per cent.) and of these seventy-four positive tests, forty (27 per cent. of the cases) were compatible with the patient's history. Rackemann insists that there must be agreement between the skin tests and the patient's history before the evidence of the skin test shall be accepted as conclusive.

BIOCHEMICAL INVESTIGATION

Not only have there been many attempts to solve the question of the nature of anaphylaxis on broad lines, but much work has also been done along special biochemical lines.

In 1913, Vaughan wrote that each protein molecule is composed of two groups, a primary or poisonous group and a secondary and characteristic group. According to Vaughan it is in this second group that proteins differ and in which their sensitizing properties lie.

Achard and Flandin [23] report that they have succeeded in isolating the poison formed during the anaphylactic state. They concluded that the poison is formed more abundantly in the nervous system than elsewhere; that it is probably a lipoid substance; that the subject is not always toxic to other animals of the species; and that its active anaphylactic properties are essentially heterogeneous and, particularly, homogeneous.

Kahn and McNeil [24] report that the specificity of the anaphylactic reaction depends on the chemical structure of the protein molecule and that if the molecule be split, its anaphylactic specificity is lost.

To this opinion as to the catabolic nature of the anaphylactic reaction Miller [25] adds his testimony. He says that two or more

23. Achard and Flandin: Compt. rend. Soc. de biol. **83**:25, 1912.
24. Kahn and McNeil: J. Immunology **3**:277, 1918.
25. Miller: J. Immunology **1**:383, 1916.

antigens may produce the same antibody and the same antigen may produce two or more antibodies. He explains that the relation of antigen to antibody does not depend on the entire protein molecule and it so happens that various unrelated substances contain these groups and so produce a common antibody.

Obviously, if these statements are true, the explanation of such multiple sensitization by unrelated substances as seen in the second clinical case, and as has been so frequently encountered by others, may lie therein.

Jobling [26] stated in a discussion of anaphylaxis before the Society of Immunology that the lipoids, which some accuse of being actively concerned in the production of the phenomena of anaphylactic shock, can cause shock but are not able to sensitize. Wilson confirms the statement.

Saula says that there is a marked increase in soaps, fatty acids and lipoids subsequent to sensitization. He suggests that anaphylaxis may be due to increased saponification. Peterson and Jobling found that soaps injected intravenously into guinea-pigs in proper doses produce the symptoms and postmortem findings of anaphylaxis.

It has been asserted from time to time that kaolin broths, starch broths, guinea-pig serum after treatment with chloroform and ether and iodized guinea-pig serum were capable of causing anaphylactic shock and that their injection was an adequate method of studying the phenomena.

Loewit denies that these substances are capable of causing anaphylactic shock and that they furnish an adequate method of study. He finds that symptoms resulting from the kaolin and starch preparations are purely mechanical effects caused by large particles of the kaolin or starch being carried into the vessels by the injection and there producing thrombi. Likewise, the fatal effect of chloroform and ether serum is not due to anaphylaxis but to thrombi. True anaphylactic death Loewit says may occur in one of two forms—suffocation arising from bronchiospasm with secondary inflation of the lung or by peripheral or central paresis of the breathing apparatus with more or less edema and hyperemia of the lungs and more or less acute pulmonary dilation. The thoracic breathing always ceases before the abdominal.

Kleinschmidt [27] found that guinea-pigs can be sensitized per os by boiled or unboiled cow's milk and that the active factor was the milk albumin, the casein merely causing a condition of hypersensitiveness.

Weil says that in the guinea-pig anaphylactic death is due to a cellular reaction and that the serum changes play no part in it but, on the other hand, in prolonged or delayed shock in the dog striking

26. Jobling: J. Immunol. **1**:491, 1916.
27. Kleinschmidt: Monatschr. f. Kinderh. **11**:664, 1913.

alterations occur in the chemical composition of the blood. Weil has himself contributed largely to our knowledge of anaphylactic serums by his widespread researches. He states that immune serum consists of two substances, one thermolabile (precipitin), the second thermostabile (sensitizin). Heated precipitin will unite with the antigen but has lost its power of precipitating. It has lost its ergophore group and retained its haptophore. Moreover, Weil has found that precipitating serums which give a voluminous precipitate with certain concentrations of the antigen may fail to give any precipitate with still higher concentrations. This zone of absent precipitation he calls the prozone.

Disassociation of the precipitate, which probably occurs within the body, sets free antibody in a form which sensitizes passively but fails to give a precipitate reaction; but as has been stated in another place and connection, the antigen and precipitating antibody do not coexist in the same fluid without union.

The precipitate represents a complex of both factors, antigen and antibody; neither very largely destroys the other if, indeed, any destruction occurs. In this the anaphylactic process resembles the precipitation reaction in the test tube which is not accompained by the chemical destruction of either factor. It is immediate. It proceeds in the absence of complement. It requires relatively large amounts of antibody and relatively minute amounts of antigen.

This rapid survey of the field of protein sensitization is far from complete. Many articles have of necessity been passed over, many special researches omitted. Yet it is hoped that the broad lines have been drawn so fairly as to give an honest view of the field as a whole.

SUMMARY

1. Protein sensitization is now an accepted fact.

2. Theories as to its meaning and its mechanism differ.

3. Much that has been published concerning the process lacks confirmation.

4. Much work is still necessary in allied fields, such as the diatheses and the intoxications, before full use can be made of the new cult.

5. In the meantime while accepting the principles of the cutaneous food test, interpretation must await fuller, better defined understanding of the process of protein sensitization before it can attain its greatest efficiency.

PROTEIN SENSITIZATION IN SKIN DISEASES: URTICARIA AND ITS ALLIES *

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INTRODUCTION

One man's meat is another man's poison. This venerable aphorism attests the antiquity of our practical knowledge of sensitization. The first scientists to note the phenomenon with wonder were Jenner and Magendie. The first to note it appreciatively and reflectively was Richet.[1] The first to bring it into relation with cutaneous medicine were von Pirquet and Schick.[2] The only notable efforts to apply it to diagnosis were made by Smith [3] in connection with buckwheat poisoning, and by Schloss [4] in connection with egg albumin urticaria. The von Pirquet [5] test for tuberculosis suggested a method by which sensitization to various proteins could be clinically determined. Smith and Schloss, as stated, were the first to apply the procedure with results. In the meantime, White,[6] Strickler,[7] Blackfan,[8] McBride and Schorer [9] essayed in this field, but their investigations concerned chiefly eczema and, although their enthusiasm was compelling, the disease they mainly

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1. Richet: Anaphylaxis; Bligh's Translation, London, University Press, 1913.
2. Von Pirquet and Schick: Die Serumkrankheit, Leipzig, 1905.
3. Smith: Arch. Int. Med. **3**:358, 1909.
4. Schloss: A Case of Allergy to Common Foods, Am. J. Dis. Child. **3**: 341 (June) 1912.
5. Von Pirquet: Allergy, Arch. Int. Med. **7**:259 (Feb.) 1911; **7**:283 (March) 1911.
6. White, C. J.: Two Modern Methods to Be Employed in the Treatment of Chronic Eczema, J. A. M. A. **68**:81 (Jan. 13) 1917.
7. Strickler, A.: Anaphylactic Food Reactions in Skin Diseases, New York M. J. **104**:198 (July 29) 1916.
8. Blackfan: Cutaneous Reactions from Proteins in Eczema, Am. J. Dis. Child. **11**:441 (June) 1916.
9. McBride and Schorer: Erythematous and Urticarial Eruptions Resulting from Sensitization to Certain Foods, J. Cutan. Dis. **34**:70 (Feb.) 1916.

dealt with has no place in this paper, except where a liaison is established by factors common to the dermatitis and urticaria groups.

The similarity of serum sickness to urticaria is striking. Von Pirquet and Schick's work suggested that all urticaria was an anaphylactic manifestation. Osler's studies on the syndrome of toxic erythema, wheals, purpura and bronchial asthma in the later light of Richet's publications further substantiated the belief. The widely recognized fact that some foods, particularly strawberries, bivalves, and crustacea invariably provoked urticaria in certain persons, added to the growing edifice. In his case of buckwheat poisoning, Smith made percutaneous tests with the offending substance and produced local reactions. Schloss tested a patient with egg white urticaria in a like manner and with like results. The evidence for anaphylaxis seemed complete. Protein extracts of nearly all foods have been manufactured and percutaneous tests have been made with them. The purpose of this paper is to discuss whether, by means of this procedure, it is possible to detect the determining factor or factors in urticaria and kindred dermatoses.

Of fifty-three cases of urticaria, fifteen of which were chronic, studies were made in fourteen of the latter. Cases 7 and 11 were observed only as to their response to suprarenal extract. The other twelve were analyzed in this respect, as well as in relation to the cutaneous reactions. The time required for careful tests, their reading and interpretation, together with the difficulty of cooperation on the part of patients, precluded a more extensive series. Intensiveness of study is offered instead. As the work progressed, it rapidly became evident that the method was difficult to pursue and apply, and that it would offer but little to those in quest of a simple and direct means to isolate the cause or causes in individual cases of urticaria. There were numerous inconsistencies. It was not clear that allergy alone explained all cases. In short, the method proved either too much or too little, so that finally there took form in our minds certain questions. To answer these the work was and will be continued. Briefly, the problems appear to be as follows:

1. Are urticaria and allied conditions, notably angioneurotic edema, anaphylactic?
2. Do positive tests prove them to be anaphylactic?
3. If not, what may be their nature?
4. If not, what do the tests signify?
5. What is the practical value of the tests?
6. How are they to be clinically applied?

For purposes of reference, the cases studied are here recorded. Only the positive points have been noted, with a summary of its salient features after each history, and a short summing up of some general

facts necessary for practical purposes. This paper aspires to avoid the onus of being of the case report type, but rather to outline what is known and to indicate what should be studied in connection with a most important dermatosis. Only positive reactions have been mentioned, but tests were made with all other foodstuffs consumed by the patient, and in certain instances with other substances, such as serum, epidermal substances, namely, feathers, hair, etc., and bacterial proteins.

REPORT OF CASES

CASE 1.—Mr. L. A., aged 54, actor. Illness six months' duration. Sudden swelling of eyelids.

Diagnosis.—Angioneurotic edema. Supposed by patient to be due to light used in acting for screen pictures. He employed a "makeup" of a red and yellow grease paint and a brown powder.

Tests were made with the last two: red paint +++, yellow paint ++, powder —, cheese +++, coffee +++. Food tests made of substances ingested on day prior to last attack. In order to check up pathogenicity of positive substances, patient applied his make-up, and within an hour and a half his eyes began to smart and swell. Ingestion of suspected foods caused no reaction.

Therapy.—Suprarenal extract instillations in conjunctival sac to reduce swelling, and one hypodermic injection of 5 minims of this substance. Elimination of grease paint.

Result.—Cure.

Analysis.—Parenteral sensitization. Numerous positive responses checking up with suspected substances. Influence of suprarenal gland extract.

CASE 2.—H. O. B., a man, aged 54, merchant. A seborrheal dermatitis of several years' duration. Several weeks sudden swelling of eyes. As a boy eggs and veal had caused headache.

Diagnosis.—Angioneurotic edema.

Tests.—Egg yolk +++, egg white —, pork +, tomato +, veal +++, walnut +.

Therapy.—Rigid diet. Suprarenal gland extract both in conjunctiva and hypodermatically.

Result.—No severe recurrence for seven months.

Analysis.—Numerous positive tests. Effect of suprarenal extract. Group reaction between walnut and egg (?). Cure by removal. (On an ocean journey patient ate egg and veal with immediate recurrence.)

CASE 3.—D. K., a man, aged 66. Disease of four weeks' duration. Sudden swelling of eyes on Wednesday mornings; ate buckwheat cakes Tuesday evenings.

Diagnosis.—Angioneurotic edema.

Tests.—Buckwheat +++.

Therapy.—Suprarenal extract, conjunctival instillations. Elimination of buckwheat from diet.

Result.—Cure.

Analysis.—Single specific reaction. Elimination and cure.

CASE 4.—Mrs. A. B., a woman, aged 65. Recurrent attacks of urticaria for three months. Indigestion and constipation for three years. Urticarial lesions associated with facial angioneurotic edema lasting from one to three days. The urticaria comes at 2 a. m., the angioneurotic edema toward evening.

Diagnosis.—Urticaria and angioneurotic edema.

Tests.—Beans ++, beet ++, cabbage ++, pork +, potato +, onions +++, oats, rice, rye, tomato, walnut + each. Confirmatory tests on cabbage and potato.

Therapy.—Cathartics, two colon irrigations; two suprarenal gland injections. Removal of positive foods.

Result.—Improvement within ten days. Very few wheals; no itching.

Analysis.—Intestinal derangement, numerous positive tests, influence of suprarenal extract. Possibly successive sensitizations. Improvement by removal of suspected foods.

CASE 5.—Master M. C., aged 9; urticaria four years before. Annual recurrence; recent attack five days' duration. Associated by mother with eating of salmon. Marked constipation.

Diagnosis.—Urticaria.

Tests.—Salmon +; all other foods —. Salmon fed to child produced no attack.

Therapy.—Removal of salmon, but lesions had already begun to involute without treatment.

Result.—Spontaneous cure.

Analysis.—Abnormal digestion. Reacts to one food. This food apparently bears no causal relation to disease.

CASE 6.—Mr. W. F., aged 29, merchant. Disease of five months' duration, beginning suddenly after attack of acute indigestion. Spleen and glands in general enlarged since childhood. Wassermann test, blood count and search for plasmodia, all negative.

Diagnosis.—Chronic urticaria.

Tests.—Beef +++, cabbage ++, casein +++, carrots +++ and ++++, cheese +++; corn ++; lamb +++; whole milk +++; veal +++; wheat glutein ++, wheat gliadin and globulin +. Patient noticed that his attacks were precipitated only by carrots when the suspected foods were eaten serially, experimentally to corroborate the cutaneous tests.

Therapy.—Colon irrigation without improvement. Suprarenal extract injection, 7 minims every five days, for five injections. Slight improvement. Elimination of suspected foods, particularly carrots.

Result.—Now without attacks for three months with only carrots removed from diet.

Analysis.—Successive sensitization. Group sensitization; specific. Offending food corroborated by diet. Treatment of digestive tract. Influence of suprarenal extract. Cure by removal of carrots.

CASE 7.—Miss E. F., aged 21. Chronic urticaria six months' duration. Six minims suprarenal extract, complete relief at once. Well from January 25 to Aug. 6, 1917. Recurrence. Suprarenal extract injected August 6, 8 and 13. Well for two months. Not observed after this.

Analysis.—Effect of suprarenal extract.

CASE 8.—Master M. K., aged 4½. Urticaria six months.

Tests.—Barley, beef, bluefish, wheat ++++ each; whole egg and rice + each.

Analysis.—Group reaction.

CASE 9.—Mr. A. M. D., aged 22.

Diagnosis.—Recurrent urticaria for four years.

Tests.—Tomato ++++.

Therapy.—Elimination from diet of tomatoes.

Result.— Well in four days.

Analysis.—Single specific reaction. Cured by removal.

Case 10.—Mrs. C. M., aged 31. Ill for two years; constipated.

Diagnosis.—Urticaria.

Tests.—Cod, pork, corn, coffee and tea ++ each; coco, coffee, lamb, lettuce and wheat + each.

Therapy.—Elimination of suspected articles from diet, on Jan. 21, 1920. Well for a week. Recurrence, with symptoms of acute gastritis. Diet continued. Free from urticaria for another week. March 5 slight recurrence.

Result.—Improvement but no cure on diet modified according to tests.

Analysis.—See result; also indigestion. Sensitization to several proteins. Group reactions.

Case 11.—Mrs. H. N., aged 50. Urticaria for four weeks. One injection suprarenal extract; well for three years.

Analysis.—This case illustrates the use of suprarenal extract; the lesions vanished within five minutes after the injection.

Case 12.—Miss E. P., aged 18. Ill for two and a half months; constipated.

Diagnosis.—Urticaria.

Tests.—Lima beans ++++, wheat ++, beef, cheese, coffee, chicken, rice, rye + each.

Therapy.—Elimination of suspected foods; catharsis; suprarenal gland extract.

Result.—Remission for two days.

Analysis.—See result; effect of therapy; multiple reactions; group sensitization.

Case 13.—Mr. D. S., aged 70. Ill four months; constipated.

Diagnosis.—Urticaria.

Tests.—Lamb and potato +++, spinach +. Patient discontinued visits.

Therapy.—None instituted.

Analysis.—Multiple or group reactions. Collapse caused by suprarenal injection administered by previous physician.

Case 14.—Miss S. W., aged 9; ill for five years, nausea, chronic constipation.

Diagnosis.—Urticaria.

Tests.—Egg +, salmon ++. Discontinued visits.

Therapy.—None instituted.

Analysis.—Multiple reactions.

I. TECHNIC

1. *Substances and Methods Used.*—The commercial products of a large pharmaceutical firm were employed in the work. It may be assumed that these preparations are at least as conscientiously manufactured as the drugs on which physicians rely in their practice. Nevertheless, it is admitted that investigators should master the art of making their test substances themselves, as Wodehouse [10] did, in order

10. Wodehouse and Olmstead: Preparation of Vegetable Proteins for Anaphylactic Tests, Boston M. & S. J. **176**:467 (March 29) 1917. Preparation of Animal Proteids for Anaphylactic Tests, Boston M. & S. J. **177**:85 (July 19) 1917.

to be able to vouch for every aspect of their experimentation. Should it ever be shown that the commercial proteins fall short in any respect, the work herein embodied is worthless. It is impracticable both for the patient and the observer to attempt more than twenty tests at a sitting. The skin is cleansed with ether, and a minute bloodless excoriation is produced at as many points along the forearm as tests are planned. A drop of decinormal sodium hydrate solution is deposited on each excoriation, and a small quantity of the protein is rubbed in with a fresh wooden applicator for each substance. Controls are made with the alkali. At first only one control was employed, but it was noted that the controls themselves vary, those near the elbow bend being larger than those near the wrist. Thus, we decided to place four controls at equal distances from the cubital fossa to the wrist in a row parallel to those of the test. If this is not done, accurate readings are impossible, all contrary statements notwithstanding, and it will be observed that the control lesions grow progressively smaller as the hand is approached.

2. *Vagaries in the Tests.*—It might be desirable to employ emulsions of raw foods for investigation. But these would spoil, and the entire literature indicates both that foods are not absorbed through the intestine in their original physical state, and that peptones and proteoses and their parent substances interreact specifically as anaphylatoxins. What is more important is that both tests and controls exhibit numerous vagaries. At times the latter exceed the former in intensity. At times responses occur to articles never ingested. This, in itself, however, has less meaning than might be imagined, but there are certain group reactions, as in Schloss' egg albumin case, that have a definite enough explanation. In urticaria, usually, there is dermographism, a phenomenon elicited in producing the excoriations.

3. *Reading the Tests.*—Thus, the reading of the tests introduces the personal equation, and yet the tests can be read with a reasonable degree of accuracy by allowing time for traumatic irritation to vanish, and by reading carefully against the controls. The reaction shows, within from ten to thirty minutes, the following features: a wheal and a stellate erythematous zone about it. If the wheal equals that of the control, and presents no erythema, it is negative, or at the most +—; if it is half again as large as the control, it is, + positive; if twice as large, ++; if three times as large +++; or if it is but half again as large and surrounded by erythema, it is ++, and so on. A wheal twice as large as the control, with a marked erythema, is +++; and everything over the above is ++++. Of course, these standards are largely subjective, and each investigator must evolve his own scale.

Tests vary slightly in intensity from time to time, but are rarely absolutely inconsistent for a given substance. Occasionally, this is not the case, and a test which at one time is positive and a week later negative, perhaps indicates the negative or antianaphylactic phase. At times, as in Case 13, the reaction may be delayed by as much as five hours, but even in this instance, correct readings, subsequently corroborated as above, were made within fifteen minutes. Strickler and Goldberg,[11] however, considered no test positive that did not persist for forty-eight hours. They, however, used the intracutaneous method which we have not attempted. Several patients reported later developments, and so far as the percutaneous tests go, Strickler's experiences do not hold.

II. IS THE SUBSTANCE THAT ELICITS A POSITIVE LOCAL REACTION A SPECIFIC PROVOKING CAUSE OF THE DISEASE?

1. *Specificity.*—The term specific, as applied in anaphylaxis, is a trifle confusing. A distinction must be made between biologic and chemical specificity. Anaphylatoxins that are biologically unlike may be chemically similar, and thus two proteins biologically distinct, may nevertheless call forth anaphylaxis. Richet stated that when we speak of specificity, it is because the preparatory substance always coexists with the exciting substance in the organic fluids we use (see section on apotoxin, and compare with Vaughan's[12] split proteins). This fact is nicely illustrated in Schloss' case which gave positive cutaneous reactions to various egg, almond and oat derivatives. Schloss was further able to show by cutaneous tests that, related to almond proteins, were those of peach, prune and plum kernels, strawberry, pear, apple and cherry seeds, but that grape and orange seeds were not related. Related to oat were rice, barley and rye, but corn and wheat were not, etc. The implication, obviously, is a chemical identity among these numerous substances. Thus, a person sensitized to a certain protein would respond to others in a kindred chemical group, although never actually sensitized by them, as is further shown in the studies of Wells and Osborn.[13] This fact is illustrated in nearly all of our own cases by the number of foods to which the skin

11. Strickler and Goldberg: Anaphylactic Food Reactions in Dermatology, J. A. M. A. **66**:249 (Jan. 22) 1916.

12. Vaughan: Protein Split Products in Relation to Immunity and Disease, Philadelphia, Lea & Febiger, 1913.

13. Wells and Osborn: Is the Specificity of the Anaphylactic Reaction Dependent on the Chemical Constitution of the Proteids, or on Their Biological Relations, Jour. Infect. Dis. **12**:341 (May) 1913; Wells: ibid. 455 (Oct.) 1908.

responds. In Case 2, a high degree of sensitization existed against egg yolk and veal. This is consistent with the extent to which these articles figured in the man's diet. On the other hand, there are instances in which only one substance appears to be the exciting agent, as in Smith's case of buckwheat susceptibility, and in Case 3 of our series.

2. *Nonspecificity.*—Multiplicity of reactions may be explained by chemical similarities in biologically totally unrelated substances. An episode early in this study that, by its apparent absurdity almost influenced us to discontinue our investigations, may be worth citing. An orthodox Jew gave reactions to pork, oysters and sturgeon, foods forbidden by the Mosaic law. This man may have transgressed as to his observances, or may have unknowingly partaken of the forbidden foods, but it is just as likely that the inconsistency had a biochemical basis.

3. *Chemical Specificity.*—It may therefore be reasonably concluded that the substance or substances eliciting positive local reactions are the specific pathogenic agents of the disease. Specific does not necessarily mean that only one food is responsible, but indicates chemical specificity in the sense that generically unrelated substances have a chemically identical architecture. This being true, the tests seem to be clearly specific.

III. CAN THE PHENOMENON BE ANAPHYLAXIS?

1. *Literature on the Subject and Present Views.*—From the preceding it may be inferred that urticaria and allied conditions may be caused by proteins in the sense that the offenders can often be determined by eliciting a local reaction, and that removal from the dietary of the indicated foods may be curative. We are definitely, then, dealing with food poisoning of some type. Is this type of poisoning anaphylaxis? To answer the question requires an outline of the nature of anaphylaxis. Richet's conception of this phenomenon is that a specific antibody is formed for each protein substance parenterally introduced. The union of antigen and its specific antibody forms a toxic entity which Richet designates as apotoxin. The nature of apotoxin is a matter of dispute, but perhaps Vaughan's assertion that it is a split protein radical is most commonly accepted. Clinically, anaphylaxis is exhibited by a series of explosive phenomena. Wolff-Eisner was the first to include among them urticaria, a concept soon substantiated by the writings of von Pirquet and Schick. The phenomenon depends on a preparatory invasion of the body by an alien protein, an incubation period, followed by a precipitating invasion of the identical protein, whereupon promptly occur a series of objective manifestations including pruritus, dyspnea, tachycardia, convulsions, bloody movements,

involuntary micturition, urticaria, diminished blood pressure due to bleeding into the sphlanchnics, and then either recovery or death. Richet first clearly observed and described the syndrome in connection with his work with actinaria, eel and horse serum. Since that time, intensive study has been accorded the subject, and a voluminous literature has amassed itself, but in no one particular are views yet quite in unison. So far as this paper is concerned, the authors feel incapable of critical review of the subject as anaphylactologists. What follows is an impersonal exposition of the minimum that must be discussed to develop the theme at hand in its clinical aspects.

2. Similarity of Urticaria to Anaphylactic Skin Manifestations in Animals.—Barnathon [14] describes anaphylactic accidents as characteristically sudden in appearance, and gradual in disappearance, subject to the laws of preparation and precipitation above described; as followed by a prolonged period of hypersusceptibility, and as due to albuminoids or their derivatives. Weil [15] considers the phenomenon due to a true antigen-antibody reaction. Bronfonbrenner's [16] views merit consideration, but are too technical to be included. Pick and Yamanouchi, as cited by Hektoen,[17] found a thermolabile substance the cause, and considered it an antigen. It could not be destroyed in six hours, at a temperature of 60 C., but lost its antigenic properties in fifteen minutes at 100 C. It resists drying, age and the addition of many chemicals and digestive enzymes, notably diastase, pancreatin, invertin and pepsin. The substance is always generically specific, except the lens, which sensitizes to lenses of all species but never to any other tissue. According to Rosenau and Anderson,[18] the amplitude of the sensitizing dose has nothing to do with prolonging the incubation period, but sensitization may persist for 732 days after the initial dose. Thus, from the literature, it follows that anaphylaxis is a state produced by introducing into an animal a foreign protein which so alters the body that when, within from ten to twenty days, a minute quantity of the same substance

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14. Barnathon: De l'anaphylaxie alimentaire: etude clinique et experimentelle, Thèse de Paris, 1911, No. 185.

15. Weil: Anaphylaxis and Its Relation to Problems of Human Disease, Lancet-Clinic, Nov. 19, 1913. On Antisensitization with Observations on Non-Specificity in Anaphylaxis, Ztschr. f. Immunitätsforsch., December, 1913.

16. Bronfenbrenner: Specific Parenteral Digestion and Its Relation to the Phenomena of Immunity and Anaphylaxis, J. Lab. & Clin. Med. **1**:573 (April) 1916. The Nature of Anaphylatoxin, J. Exper. Med. **21**:480 (May) 1915.

17. Hektoen: Allergy or Anaphylaxis in Experiment and Disease, J. A. M. A. **58**:1081 (April 13) 1912. Precipitation Production in Allergic Rabbits, J. Infect. Dis. **21**:279 (Sept.) 1917.

18. Rosenau and Anderson: Further Studies on Anaphylaxis, Hyg. Lab. Bull. **45**: (June) 1908. Further Studies on the Phenomenon of Anaphylaxis, Hyg. Lab. Bull. **50**: (April) 1909.

is introduced, a definite syndrome is provoked. The underlying mechanism is not entirely understood, but depends on one factor or on a combination of the factors outlined. The body cells are altered to become most susceptible to a substance not inherently poisonous. The sensitization may persist for two years, as Rosenau and Anderson have shown, and the provoking substance is highly resistant to physical, chemical and digestive agents.

3. *Allergy, Idiosyncrasy, Susceptibility and Hypersusceptibility.*—After a body has been sensitized, its cells are temporarily or permanently altered in such a manner that they have become susceptible to formerly harmless proteins. In other words, their reactive powers have undergone a subtle metamorphosis. Pirquet designates this fact by the term allergy. Allergy indicates, practically, a cell hypersusceptibility to foreign proteins demonstrable by exposing the cells to small amounts of a sensitizing substance, whereupon a local, visible, inflammatory reaction arises. Pirquet called the local excitant allergen, and considered it analagous to Detre's antigen. Both in anaphylaxis and allergy periods develop in which, for reasons needing no elaboration at this point, sensitized organisms fail to respond to the precipitating substance. This phase of nonreactibility is called anergy. Antianaphylaxis is the state of desensitization.

In the preceding paragraph the word hypersusceptibility was employed. Hypersusceptibility, as Hektoen explains, is not synonymous with anaphylaxis. In a given animal a peculiar toxic reaction, depending on uniformity of the offending protein, is hypersusceptibility. In anaphylaxis, which is the result of sensitization, no matter what proteins are employed the symptoms are constant. Von Behring,[19] who noted anaphylaxis in horses against the bacillus of Nicolaier, and of various animals to diphtheria antitoxin, termed the phenomenon hypersusceptibility. This is untechnical usage in the modern sense. Anaphylaxis, then, is an artificial and restricted form of induced hypersusceptibility—a condition *sui generis*. Hypersusceptibility cannot be transmitted artificially to normal animals (it is a congenital characteristic), while anaphylaxis is transmissible. Idiosyncrasy is a broad and ill-defined term. It signifies an unusual body response to a substance. A person rendered restless by morphin, or one who gets an erythema from arsenic, has an idiosyncrasy to these substances. So, too, one who is nauseated by a given food without sensitization. Susceptibility signifies the normal tissue response to given substances, such as increased vascular tone, perhaps, to digitalis. Hypersusceptibility

19. Von Behring: Allgemeine Therapie der Infektionskrankheiten, Lehrbuch der Allgemeinen Therapie, Wien., 1899. Von Behring and Kitashima: Ueber Veminderung und Steigerung der ererbten Giftempfindlichkeit, Berl. klin. Wchnschr. **38**:157 (Feb. 11) 1901.

is an idiosyncrasy when not anaphylactic. When anaphylactic, if the word hypersusceptibility may be employed at all, it signifies an acquired characteristic due to artificially induced, definite body alterations. Hair splitting as these distinctions must seem, since in technical usage they have acquired definite significance, their definition must be understood.

4. *Anergy.*—To revert to the question of anergy alluded to above: If a sensitized animal, as Besredka, Nicolle and Otto and numerous others have amply demonstrated, be reinjected before the incubation period is complete, anaphylaxis does not take place. Also, shortly after anaphylactic shock, if animals are reinjected, the phenomenon fails to appear. Thus, by injecting at too short intervals for anaphylactic manifestations to recur, the animal can be rendered immune. In other words, it has become desensitized, and it is widely accepted that immunity and anaphylaxis are one in mechanism and significance. The state after anaphylaxis which is free from reactability to the alien protein is what von Pirquet designated as anergy.

4. *Nonprotein Substances and Anaphylaxis.*—Curiously enough, substances not proteins are capable of producing a condition at least simulating anaphylaxis. It is too fresh in the minds of physicians to need emphasis that arsphenamin is one of these, as pointed out by Homer Swift. Adercco [20] found a similar state of affairs in animals in the experimental use of cocain. The possibility of cumulative effect, however, must not be overlooked. On the other hand, it is conceivable that chemicals may alter body proteins of the host in such a manner as to convert these, in effect, into alien proteins capable of producing anaphylaxis. No experimental evidence of this exists.

5. *Humeral and Cellular Theories.*—The final scene of the anaphylactic phenomenon is the cell, but it has not yet been positively decided whether the entire action takes place there, or whether its earlier phases occur in the body juices, subsequently to be transferred to the cell for the dénouement. Thus, two schools exist, one favoring the cellular, the other the humeral theory. There is a third which records the entire process as physical. We do not pose as arbiters in the debate. As a matter of fact, so far as our theme is concerned, it makes no difference which view is academically correct, for in the final analysis, it is the cell that is affected.

6. *Clinical Mechanism of Sensitization: The Portal of Entry Intestinal.*—Thus far, mainly abstract questions of anapyhlaxis have been discussed. If urticaria is an anaphylactic phenomenon due to food sensitization, the question arises whether alimentary sensitization can

20. Adercco, V.: Action plus intense de a cocaine quand on en répète l'administration a courte intervalle, Arch. Ital. de Biol. **20**:32, 1896.

take place. Normally, only amino acids permeate the intestinal wall; peptones and proteoses do not. Amino acids cannot cause anaphylaxis. Peptones and proteoses can, and they react biologically specifically with their parent substances, or chemically specifically with related substances, as brought out in Schloss' work. Thus, it is necessary to inquire whether peptones and proteoses ever enter the circulation through the intestine. If they do, can they accomplish this through a normal intestine, or must there be an organic or functional derangement to permit this? Obviously, foods in their original chemical state are rarely assimilated. For such absorption, however, the proteins must be in solution, or at least partly hydrolyzed. Hektoen states that sensitization has been experimentally produced in guinea-pigs by the "inhalation of a fine spray of foreign serum." It is possible that some of the inhaled protein may have reached the stomach; it is also likely that some inhaled pollens reach the stomach in asthmatics and in victims of hay fever. But the supposition generally held in the latter conditions is that the protein is absorbed through the bronchial mucosa. Since there are no ferments in the latter, we may assume, with reason, that the protein is absorbed in its natural state. The inference, as it relates to the gastro-intestinal mucosa, is obvious. Furthermore, sensitization can be accomplished by rectal injection in animals, indicating absorption of unchanged protein through the alimentary mucosa.

Barnathon has exhaustively analyzed these considerations. He points out, assuming the possibility of intestinal sensitization, that patients presenting the condition are habitually troubled with constipation, or enteritis, or enterocolitis or diarrhea, and that even small amounts of precipitating doses enterally absorbed, cause the phenomenon precisely as in experimental parenteral anaphylaxis. He was able to cure urticaria in a young woman whose attacks were caused by shell fish and accompanied by vomiting and diarrhea, when he prescribed pepsin and hydrochloric acid for her achlorhydria. Arthus, cited by Barnathon, introduced antigen rectally into a rabbit, and seventeen days later elicited anaphylaxis by injection. Bouteil [21] injected the preparatory dose into the portal and mesenteric veins of dogs and rabbits, and produced anaphylaxis after a suitable incubation period. Nobecourt [22] sensitized rabbits to egg white by gastric and rectal injection. Barnathon concluded that alimentary sensitization could occur and was due to absorption of proteins incompletely hydrolyzed because of some disturbance of the digestive juices. In dogs, previously sensitized to egg white, he was unable to obtain toxic effects

21. Bouteil: Des voies d'introduction des substances anaphylactisantes, Thèse de Paris, 1910.

22. Nobecourt, P.: Mortalité des lapins sounis a des injections de blanc d'oeuf, Compt. rend. Soc. biol. **66**:850, 1909.

by injecting that substance, digested for forty-eight hours by pancreatin in an incubator.. Van Alstyne,[23] experimenting with dogs, proved that egg albumin introduced into the stomach or intestine (except the duodenum) passed into the blood. With proper controls, she obtained anaphylactic shock with a dog's blood (so prepared) in guinea-pigs sensitized to albumin. She duplicated these results by feeding egg white by gavage, thus not injuring the alimentary tract. In her first series of experiments she had ligated the intestine to form a cul de sac. With milk, and horse and beef serum she reproduced both series of experiments. Ligation of the duodenum gave no consistent findings, nor did edestin give consistent results. She concluded that protein was absorbable unaltered through intact alimentary epithelium, but that trauma favored the phenomenon. She decided that conditions interfering with digestion increase absorption of unaltered protein, and applied her views particularly to urticaria. Ganghofer and Langer [24] showed that in animals under eight days old, in massive doses, the gut was permeable to alien proteins, and in two debilitated infants undigested egg white was demonstrated in the blood by precipitation tests. In this connection, be it particularly noted for future reference, that Cannon [25] observed that the alimentary canal is highly adaptable in its function. Experimentally he found that the saliva of dogs feeding on a rich carbohydrate diet acquired marked amylolitic powers, and that animals, when enraged, showed diminished intestinal peristalsis.

Uhlenhuth [26] found that prolonged feeding of egg to rabbits produced specific precipitins in their blood, and Ascoli [27] was able under the conditions mentioned to determine its presence in the blood within three quarters of an hour after ingestion. Vaughan, Cummings and McGlumpy [28] demonstrated by anaphylactic tests, that rabbits absorb incompletely digested protein through the alimentary tract. Schloss and Worthen,[27] by applying the facts recited, determined that such

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23. Van Alstyne, E. V.: The Absorption of Protein without Digestion, Arch. Int. Med. **12**:372 (Oct.) 1913.

24. Ganghofer and Langer: Ueber die Resorption genuiner Eiweisskorper im Magendarmkanal Neugeborener Tiere und Säuglinge, München. med. Wchnschr. **51**:1497, 1904.

25. Cannon, W. B.: Recent Advances in the Physiology of the Digestive Organs, Am. J. Med. Sc. **131**:563 (April) 1906.

26. Uhlenhuth: Neue Beiträge zur Spezifischen Nachweiss von Eierweiss auf biologischem Wege, Deutsch. med. Wchnschr. **26**:734, 1900.

27. Ascoli in Schloss and Worthen: The Permeability of the Gastro-Intestinal Tract of Infants to Undigested Protein, Am. J. Dis. Child. **11**:342 (May) 1916.

28. Vaughan, Cummings and McGlumpy: The Parenteral Introduction of Proteids, Ztschr. f. Immunitätsforsch. **9**:16, 1911.

substances appeared in the urine. In normal infants they found that imperfectly digested proteins were absent from the urine, but were present in infants with gastro-intestinal disturbances which evidently favored assimilation of incompletely digested proteins.

As to clinical medicine, the practical inferences to be drawn from the statements made above are numerous. The intact intestine, as shown by Van Alstyne, may be capable of assimilating unaltered protein, and as shown by Arthus, is capable of assimilating altered protein. Abnormal intestinal mucosa, as indicated by Barnathon, is capable of this, and he includes in his conception of disturbances, those which are functional as well as anatomic. Bouteil's findings confirm this, as do those of all other authors cited. Schloss and Worthen, by their studies of infants, bring the work on animals into relation with human problems of sensitization, and Van Alstyne specifically applies her results to urticaria. It is perhaps speculative to remark here that the flora of the intestine, biliary disturbances, the free consumption of alcohol, spices and acid substances, may so influence the alimentary mucosa as to alter its permeability, or so influence the function of digestion as to alter the character of the proteins. By either means, or a combination of them, sensitization is as likely to occur in human beings as in animals. Herein lies probable clinical substantiation of experimental evidence. In this connection, emotional and nervous instability or strain may, in man, produce the digestive disturbances mentioned by Cannon as occurring in animals. Thus, may be accounted for practically the frequent occurrence of urticaria in neurotic and vagotonic persons.

So far as it is possible to translate human statements and physical signs into terms of morbid biology, with special reference to sound clinical medicine, many of our patients present features consonant with the ideas expressed in the foregoing paragraphs. Intestinal disturbances occurred in Cases 4, 5, 6, 10, 12, 13 and 14, a total of seven in fourteen. As a rule, the complaint was constipation. At times, nausea, vomiting, or diarrhea were found. In a woman, not included in this series, mucous colitis had existed for ten years, and the urticarial attacks began with vomiting.

7. *Clinical Mechanism of Sensitization: The Portal of Entry Parenteral.*—In experimental anaphylaxis it has been shown that the portal of entry may be either enteral or parenteral, and in human anaphylaxis it is clear that, when not artificially produced, as by serum injections, it is mainly enteral. Can it be parenteral? Pirquet and Schick state that guinea-pigs may be sensitized by inhaling sprayed foreign serum. In Schloss' patient, mere contact of egg with the lip produced urticaria. It is conceivable, however, that substances entering the mouth might have to be swallowed before being absorbed. In this connection it may

be remarked that such small amounts of alien protein may sensitize (1/1000,000 gm. egg white; Wells working with guinea-pigs), that sensitization through injured integument is conceivable. This entire question has not yet been adequately investigated.

If Case 1 of our series actually is an example of allergy, sensitization must have been parenteral, for the offending substances had been applied mainly to his eyelids. These substances gave positive local reactions percutaneously, and when, for purposes of corroboration, he applied the pigments to his lids, itching, burning, and slight swelling appeared within an hour and a half. Nothing is known of sensitization through normal integument, but it is possible that the skin at these sites always presents microscopic injuries, particularly in people applying cosmetics. This patient will receive further study.

8. *Clinical Mechanism of Sensitization: Hereditary, Congenital and Spontaneous Occurrence; Transmission Through Maternal Milk.*—Longcope [29] believes that hypersusceptibility is hereditary and at times spontaneous. Pirquet has shown that it may be congenital, for it is found in the offspring of anaphylactic animals shortly after birth. This, however, is merely an example of passive sensitization. Barnathon cites Hutinel's [30] observation of sensitization transmitted passively through human milk to nursing infants. The concept of hereditary anaphylaxis is difficult to grasp, unless acquired characteristics are transmissible. If the peculiarity was congenital in the first generation, it could be transmitted via the chromosomes, but this would be an example of hereditary transmission of a congenital variation, a concept conforming to our knowledge of the laws of heredity. If congenital in the first generation, and not acquired, the phenomenon would not be anaphylaxis, but hypersusceptibility or idiosyncrasy; for, having started spontaneously, it could not be construed strictly as anaphylaxis. Transmission of sensitization to offspring, or through the milk, are sound examples of the passive form, but are transitory, and the former variety has nothing to do with heredity.

9. *Influence of Drugs and Chemicals on Anaphylaxis.*—Banzhaf [31] and Steinhardt have shown that chloral inhibits anaphylactic shock, while lecethin does not. Stokes pointed out the value of atropin as a prophylactic in acute arsphenamin reactions, particularly of the type designated anaphylactoid by Swift. It is, of course, not quite clear how arsenic can cause anaphylaxis, but a discussion of this problem appears in an earlier passage (III, 4), and need not be repeated. The

29. Longcope: Susceptibility of Man to Foreign Proteids, Am. J. Med. Sc. **152**:625 (Nov.) 1916.

30. Hutinel: Intolérance pour le Lait, La Clinique, April, 1908.

31. Banzhaf and Steinhardt: Vaughan's Split Products and Unbroken Proteins: A Comparative Study of Their Effects, J. Med. Res. **23**:5, 1910.

usefulness of suprarenal extract in inhibiting anaphylaxis is widely known, and will again be alluded to in an entirely different phase, particularly in its special application to urticaria. As Sâmberger [32] points out, the wheal is primarily due to a dilatation of vessels, and suprarenal extract narrows them. The chemical mechanism of this will be further explained later. Undeniably, suprarenal gland extract usually limits individual outbreaks of wheals, and at times controls urticaria completely. In our experience, the calcium salts are utterly valueless.

Suprarenal gland extract is most efficacious when employed hypodermatically. Its administration by mouth seems futile, for it does not survive alimentary digestion as an efficacious substance. In employing it, the possibility of cardiac collapse must be remembered, and if results are not obtained after one or two injections, they will not be obtained. H. Miller's suspension in olive oil is less toxic and seems no less efficacious than aqueous solutions. Its absorption is more gradual, and hence smaller amounts of the drug may be employed, with practically no risk to the heart. Instillation into the conjunctival sac promptly reduces the swelling of the eyelids in angioneurotic edema of these organs. This was observed in Cases 1, 2 and 3 of our series. In Cases 4, 6, 7, 10, 11 and 12, it was used with uniformly good results. In Cases 5, 8, 9, 13 and 14, it was not employed, either because of the youth of the patient, or because our studies had not sufficiently advanced, or, as in Case 13, because the drug was known to act badly. The patient in this instance, a man of 70, had been given an injection of the gland extract by another physician and had collapsed. Cases 7 and 11 were included in our series to illustrate the effect of the drug. The patient in Case 7 was a young woman whose first relief in six months immediately followed an injection. She remained well thereafter, as the history shows, for seven months. The second patient was a woman of about 50 who, after constant urticaria for four weeks, was cured within ten minutes of her injection, and has since remained well for a period of three years. Knowing that suprarenal gland extract curbs anaphylaxis, and that it often curbs urticaria, have we here evidence that urticaria is an anaphylactic phenomenon? Have we here the elements of axiom one? Have we a syllogism or a sophism?

10. *The Nature of the Anaphylatoxin.*—Proteins in their original state as ingested may be anaphylatoxic, and furthermore, parent substances react specifically with their derivatives, as repeatedly stated. What, then, are these products? Magendie noted the egg phenomenon in 1839, but could not explain it. Rosenau and Anderson, working

32. Samberger: Die Entzündliche und Urtikarielle Hautreaktion, Dermat. Wchnschr. **61**:739 (July) 1915. Weitere Erfahrungen über die lymphatische Hautreaktion, Dermat. Wchnschr. **65**:623, 1917.

with horse serum, noted that its toxic properties disappeared when heated at 100 C. for an hour, but could not confirm Besredka's observations that this substance lost its sensitizing properties through age. Fleischmann [33] digested beef serum with trypsin until the Biuret test failed. Such serum loses its precipitins, and this was further substantiated by Moreschi, Neisser and Sachs by means of the Bordet-Gengou test. However, in the course of digestion, preceding the loss of the Biuret reaction, substances capable of producing anaphylaxis exist. Werbitski [34] thus was able to elicit shock in guinea-pigs sensitized to serum by reinjecting peptones derived from like serum by digestion. Richet corroborates this in the statement "as long as the albuminoid molecule is not completely destroyed, even when it is broken up by tryptic digestion, it remains capable of producing anaphylaxis." Zunz [35] proved that primary proteoses could cause both active and passive anaphylaxis, but not thio-albuminose, or other so-called proteoses, Siegfried's pepsin, fibrin, peptone-beta, or any abiuret products of peptic, tryptic or ereptic digestion. Animals sensitized to hetero-proteose, protoproteose or synalbuminose (the primary proteoses) develop anaphylactic shock on reinjection with the original serum, hetero-albuminose or proto-albuminose. This does not occur with synalbuminose, thio-albuminose, or any abiuret products of any form of digestion. Hetero-albuminose and proto-albuminose sensitize and precipitate anaphylactic shock, while synalbuminose only sensitizes. It follows, therefore, that sensitization and the production of anaphylactic shock are due to different groups in the protein molecule. Pirquet long before, in the early days of anaphylaxis, stated that not all albuminoids were allergens, but that peptones acted weakly and leucin and tyrosin not at all.

Thus original proteins and their digestive derivatives, up to a certain point, are admittedly capable of intersubstitution, in the anaphylactic sense. After a certain point in cleavage, however, this no longer obtains. Moreschi, Neisser and Sachs, as quoted by Fleischmann, proved that amino acids could not be antigens. Pirquet's observations as to leucin and tyrosin apply here, as do Zunz's regarding any protein cleavage products beyond the biuret stage. Barnathon states that proteins of advanced decomposition, particularly leucin and tyrosin, do not cause anaphylaxis. Schloss and Worthen say "it has

33. Fleischmann: Ueber die Prazipitogens Eigenschaft trypsinverdaute Rinderserum, Ztschr. f. klin. Med. **59**:515, 1906.

34. Werbitski: Contribution à l'étude de, l'anaphylaxie, Compt. rend. Soc. de biol. **66**:1084, 1909.

35. Zunz: Contribution a l'étude de la digestion et de la resorption des proteins dans l'estomac et l'intestin grêle chez le chien, Mém Curonnés **20**:3, 1908.

been demonstrated that specificity is lost in protein cleavage products lower than the peptones." Saunders [36] implies all of the foregoing with regard to the effect of egg albumin and milk.

Thus sensitization is produced by proteins down to, but exclusive of, the amino acid stage. The conception depends on two factors as illustrated in the split protein conception of Vaughan, Zunz and others. According to Hektoen, in sensitization, bodies of the general nature of amboceptors are formed which are specific, and after uniting with complement and antigen, produce anaphylactic symptoms and lesions. This action depends on protein digestion, as seen after the injection of Witte's peptone, a split protein. Vaughan thinks a ferment exists in the organs of sensitized animals, capable of splitting protein. Bruck's [37] experiment practically substantiates all of this. He passively sensitized a guinea-pig with human serum of a person reacting to pork and produced anaphylaxis by a second injection of hog's serum.

Anaphylatoxins are proteins capable of withstanding heat of 100 C. for an hour, or peptones, or proteoses derived from these, or split proteins such as Witte's peptone. But no protein derivatives are among these that no longer give the Biuret reaction. The parent substances, and their derivatives, obtained by any type of digestion whatever, or chemical splitting, interplay in producing sensitization or precipitation, and are capable of provoking active or passive anaphylaxis. One element of the split protein acts generically, and the other specifically, and so far as the body is concerned it is conceivable, as Vaughan states, that in the last analysis anaphylaxis depends on protein-splitting ferments in the sensitized body.

11. *Demonstration of Sensitization by Local Reactions.*—Schloss' case of egg albumin urticaria, Wolff-Eisner's impression of this disease, Smith's case of buckwheat poisoning, amply illustrate the fact that allergy exists in the tissues of sensitized persons. These authors further show that it is demonstrable by local tests. As Vaughan indicates, the higher mechanism of immunity and anaphylaxis are identical, and in a similar fashion it is clear that all nutrition and immunity being in the same category, sensitization must bear a relation to nutrition equivalent to its relation to immunity. The curious fact remains that since urticaria is anaphylactic, local reactions may be elicited by so many substances in each case. This is explained by facts outlined earlier. In the first place, a person may be actually sensitized to more than one food, just as an animal may experimentally be sensitized to several substances. Second, specificity is chemical, as well as biologic,

36. Saunders: Serum Disease as a Clinical Manifestation of Anaphylaxis, Interstate M. J. **15**:576, 1908.

37. Bruck: Experimentelle Beiträge zur Aetiologie und Pathogenese der Urticaria, Arch. Dermat. u. Syph. **96**:241, 1909.

and proteins fall into related groups as has been shown by Schloss (II, 1) and as follows from the studies of Banzhof and Steinhardt. As a matter of fact, in our series, Cases 2, 4, 6, 8, 9, 10, 12 and 13 responded to several proteins, but always with greater intensity to two, as in Case 2 (egg yolk and veal), or only one, as in Case 4 (onions), Case 6 (carrots), Case 9 (tomato), and Case 12 (lima beans). Case 8 responded intensely to barley, beef, bluefish and wheat. It will be a problem of the future to try to work out these group relationships in anaphylaxis, as only such a solution will increase the clinical value of cutaneous tests.

Perhaps the greatest practical light is thrown on multiple reactions and chemical and biologic specificity by the work of Wells and Osborn. These writers found that wheat and rye interreacted. Zein (corn) does not react to wheat gliadin, while hordein (barley) does. They continue:

> The specificity of the anaphylaxis reaction is determined by the chemical structure of the reacting proteins, rather than by their biological origin. The most reasonable explanation of these results is that both gliadin and glutein contain common groups which react with one another, and that the specificity of the anaphylaxis reaction is not dependent on the chemical makeup of the entire protein molecule.

Hordein reacts with gliadin, gliadin with glutein, but glutein does not react with hordein. Thus, probably, glutein and gliadin contain common groups. "Animals sensitized with proteins will, as is well known, react with either, and after recovery from reaction to one protein, the reaction given with the second protein is less severe."

12. *Summary.*—Different animals, as shown by Richet, present varying syndromes under anaphylactic shock, each species always presenting the same symptoms, whatever the protein used. Among symptoms of anaphylaxis in human beings, as shown by the writings of Schloss, White, McBride and Schorer, Wolff-Eisner, Pirquet and Schick, and others, may be included urticaria. Even in lower animals cutaneous manifestations, such as pruritus, occur. Anaphylaxis produces changed tissue reactions, or allergy, in the sense of Pirquet. Thus the skin may reasonably be included among the allergic tissues. It is compatible with our knowledge that sensitization may occur enterally, as well as parenterally, and thus, in human beings, incomplete products of protein cleavage may be absorbed by an abnormal intestine and sensitize the person. Sensitization of this sort is subject to the same laws as is the parenteral variety; namely, incubation, precipitation and desensitization after the shock. Even active and passive sensitization (Bruck) can be demonstrated by the serums of anaphylactic people, by means of the milk of sensitized women. The anaphylatoxin has distinct physical properties, and is both biologically and chemically

specific, the latter specificity being clinically as important as the former. It follows, since the skin is allergic, and since urticaria in general is an allergic phenomenon, that urticaria is probably an anaphylactic manifestation.

DO POSITIVE SKIN TESTS PROVE THAT URTICARIA IS ALWAYS ANAPHYLACTIC?

It is admitted that urticaria may be an anaphylactic manifestation, and that sensitization is demonstrable by local reactions or tests. Does it follow from this that positive tests prove that urticaria always is due to allergy? To discuss this we must take up several questions. 1. What is the nature of urticaria clinically, pathologically and pathogenically? 2. Is there anything in these conditions indicating anaphylaxis? 3. What is the nature of tissue reactions in general to pathogenic agents?

1. *The Nature of Urticaria Clinically, Pathologically and Pathogenically.*—Urticaria is an acute or chronic dermatosis characterized by the sudden appearance in crops of wheals. The duration of the disease may be indefinite, although the individual wheals are usually evanescent. Chronic varieties in which papules form are known and are related to prurigo. Bullous varities are related to Duhring's disease. The two last have been interpreted by Johnston and Schwartz [38] as anaphylactic manifestations. There is no substantiation of the belief. More important is the relation of urticaria to toxic dermatoses caused by drugs, unascertained factors, or appearing in general infectious diseases. The last might well be anaphylactic and of bacterial origin, but equally well might be more like drug eruptions and due to bacterial or metabolic toxins. The relationship of toxic rashes, purpura and erythema multiforme to anaphylaxis is strongly suggested in Osler's studies. An analogy between urticaria and hay fever is strikingly indicated in the writings of Robert Cooke and I. Chandler Walker, and a common bond between hay fever and urticaria is the asthma emphasized in Osler's group of diseases. That angioneurotic edema and urticaria are allied is clear from the frequency with which the former appears as a participant in the latter.

Pathologically, urticaria narrows itself down to an understanding of the wheal. Brun,[39] with egg albumin and milk, produced swellings in the ears of sensitized rabbits. True, they were not wheals, but such lesions do not develop in these animals. Undoubtedly, Schloss, Smith, Pirquet and Schick, and Longcope produced wheals locally by trauma,

38. Schwartz: Studies in the Metabolism of Dermatitis Herpetiformis, J. Cutan. Dis. **31**:994 (Dec.) 1913.

39. Brun: Contribution a l'étude de l'anaphylaxie, Thèse de Montpellier **81**: 1905.

and the application of suitable protein in poisoning by egg albumin, buckwheat and serum. Thus in urticaria, specific wheals can be produced by specific toxins. On the other hand, dermographism exists nonspecifically in urticaria, and thus excoriations alone may excite wheals. It is for this reason that specific are compared with nonspecific wheals, as controls, in making and reading the tests.

According to Kreibich,[40] wheals are due to the irritation of sympathetic cells through sensory irritants. The sympathetic ganglions are not diseased, but pathologically overfunctionate. He quotes Török [41] and Philipson, however, who considered wheals the result of toxins, and Quincke's edema is included in his generalization. More important than Kreibich's views are those of Sâmberger. He agrees with Török and Philipson to some extent, and also with Kreibich, but believes that a vasodilatation alone can produce no inflammation. Bier [42] amputated a hog's leg below a tourniquet. After removing the latter, and in spite of free hemorrhage, there was hyperemia. The explanations of Török, Kreibich and the Unna school would be inadequate to a situation in which hyperemia existed where there was a free flow of blood, as from the cut surface of the hog's amputation stump. Sâmberger, himself, thinks that the cells in the involved area have been asphyxiated, and that their oxygen hunger calls for an increased blood supply (hence, hyperemia) in order to bring more oxygen to the asphyxiated cells. Thus he concludes that capillary dilatation has this purpose. In addition, leukocytes bring nourishment to affected cells, and favoring this function is the lowered circulatory rate in hyperemia. These phenomena determine the first step in exudation, and an exudate shows the local need of cells for nutrition. In health, enough oxygen and nourishment are derived from the normally circulating blood. Exudation determines a hypersecretion of vascular endothelium, notably that of the lymphatics; and the endothelial cells, which are capable of an ameboid movement, locate themselves near disturbed tissue cells that require more oxygen and nourishment.

Hyperemia of the skin is observed in injuries by the sun, heat, mechanical agents and toxins, not through their direct influence on vasodilators, but because they thus subserve the increased need of the exposed cells for oxygen and nourishment. He regards urticaria in this category and explains the wheal on this basis. The edema of the collagen is caused by dilatation of the lymph spaces, and the wheal is not an angioneurosis but the result of an endothelial proliferation dependent on an attempt to oxygenate and feed asphyxiated and starv-

40. Kreibich: Die Angioneurotische Entzündung, Wien., 1905.

41. Török and Hari: Experimentelle Untersuchungen über die Pathogenese der Urticaria, Arch. f. Dermat. u. Syph. **65**:21, 1903.

42. Bier: Mares Physiology, Part 3, Division 2.

ing cells. The presence of mast cells proves this, and a wheal represents a compensatory hypertrophy of tissue and an increase of function designed to satisfy an imperative local need. He characterizes the wheal as a "secretory anomaly of lymph" or what he calls "a lymphatic hypersecretory efflorescence." He makes his classification more extensive than this paper requires, even including therein pemphigus. He distinguishes between ordinary and urticarial inflammation, stating that the same cause may incite in one person the former, and in another the latter, and that this rule applies to all injurious substances and traumas.

In his second paper he continues with the idea that the angioneurotic reaction, better called the "lymphatic skin reaction," is primarily due to anaphylaxis. He analyzes, in case reports, the relation between urticaria, diarrheas, weakness and asthma and discusses the rôle of vagotonia and sympathetic disturbances to the disease. Thus, he allies the mechanism to the ductless gland system. He calls anaphylaxis vagotonia acutissima, and serum sickness vagotonia acuta. In this sense he regards urticaria as an endocrine disease in which the vagus dominates the sympathetic system. In the final analysis anaphylaxis causes local asphyxia and malnutrition; wherefore, hyperemia, exudation and an endothelial hyperplasia develop. In other words, because of sympathetic paralysis as artificially produced by Claude Bernard, who elicited sympathetic ischemia by extirpating the cervical gland, the blood is locally squeezed out of the tissue in urticaria. Hence, an increased demand for oxygen is registered in the form of a final hyperemia and wheal formation. Administration of suprarenal gland extract in urticaria cured several of Sâmberger's cases. Gradinescu extirpated suprarenal glands in animals and found that the lymph flow from the thoracic duct was increased. Sâmberger thus concludes that since suprarenal extract increases the circulatory rate by narrowing the capillaries, it prevents anaphylaxis, and causes involution of wheals by the resultant increase of oxygen content in the asphyxiated cells.

Sâmberger's theory may be overnice, but it is so far in conformity with experience that his objective observations are correct. The wheal is due to the exudation. The mast cells definitely indicate the need for hypernutrition. The collagen is swollen. Suprarenal gland extract causes the wheals to involute. Whether the entire process depends on asphyxia or not, we cannot state, but whatever Sâmberger's explanation, there is something fundamental in his concept.

2. *Indication of Anaphylaxis.*—Consensus of opinion favors the belief that suprarenal gland extract inhibits anaphylactic shock. Its place in urticaria is established beyond doubt. Does this indicate that urticaria is anaphylactic? Sâmberger holds that any agent, physical, chemical, or toxic, can produce cell asphyxia, that cell asphyxia determines the wheal, and that the wheal disappears when oxygenation is

re-established, as by the effect of suprarenal gland extract. If these views are correct, wheals can be produced otherwise than in anaphylaxis, an suprarenal gland extract, because of its utility in urticaria, would not necessarily prove that the latter is anaphylactic. The effect of suprarenal gland extract in our cases, both of angioneurotic edema and urticaria, has been recorded (III, 9).

Unquestionably dermatitis venenata, some forms of which have groundlessly been considered anaphylactic, does not respond to suprarenal gland extract. Neither do these forms give positive cutaneous reactions, and nevertheless, some confusion exists as to this group. Urticarial elements, small lesions suggesting wheals, have been seen in all types of acute dermatitis. Urticarial lesions have been described in syphilis, particularly by Hazen and Sutton, and nevertheless no percutaneous responses exist in this disease, nor does suprarenal extract cause their involution. Wechselmann thought his case of satinwood dermatitis anaphylactic. The urticaria caused by the nettles is apparently not anaphylactic, and the exciting agent in primrose dermatitis, as shown by Simpson, is not a protein. In short, syphilis, nettle, primrose, rhus, and other forms of dermatitis venenata may have urticarial lesions, but these are not anaphylactic in causation. They do not respond to suprarenal gland substance, and, so far as our experience goes, no type of urticarial lesions, except those of presumably anaphylactic origin, give cutaneous reactions, or respond to suprarenal extract.

3. *Nature of Tissue Reactions in General to Pathogenic Agents.*—Whereas, in general, urticaria is perhaps justifiably considered anaphylactic, it is reasonable to suppose that other pathogenic agents, as shown above, may cause similar tissue responses. It has already been noted that wheals at times are seen in syphilis and various forms of acute dermatitis of known and unknown causation. Thus the wheal alone does not indicate anaphylaxis. On the other hand, a dermatosis characterized by wheals and giving a percutaneous protein reaction may be reasonably certainly regarded as anaphylactic, for such reactions are not encountered save in diseases due to sensitization. No toxin of any sort, of itself, causes disease. Disease is just as much a matter of tissue response, as of a pathogenic agent, and depends on an interplay of the two. Thus, no disease can arise without tissue hypersusceptibility. In this sense there is nothing peculiar about urticaria; but it is peculiar to urticaria that the special mechanism is one of general sensitization, a condition registered in given cells as allergy which can be demonstrated by a special test, not known except as to allergy. In other words, in urticaria a tissue reaction is provokable by the local application of small doses of chemically or biologically specific toxins. Without dogmatizing then, although wheal-like lesions exist in diseases not urticarial, and clearly not due to anaphylaxis, that

disease which is called urticaria may be regarded as being so, among other reasons, because evidence may be adduced of its anaphylactic origin by means of cutaneous tests.

V. SIGNIFICANCE OF THE TESTS

Numerous controls, the combined observations of numerous writers, indicate that positive reactions reveal a peculiarity of the person, otherwise every one would react to all protein, or no one would react to any. It need no longer be reiterated that at least in the majority of cases a percutaneous reaction indicates sensitization, while a negative test does not rule this out. This statement is not to be regarded as dogmatic. Amazing possibilities of confusion exist.

1. *Variations in the Reactions.*—A test may be negative in a sensitized person, perhaps because he has become desensitized, as has been pointed out by Longcope, or after serum sickness. Or it may be positive, as in the case of the orthodox Jew. Mechanical problems also arise. The excoriations may be too superficial, or too deep, introducing fortuitous elements into the wheal. But nevertheless the significance of tests is amenable to some criteria. If a substance indicated by the tests is eliminated from the diet and the patient recovers, as in Case 2 caused by veal and egg yolk, Case 3 caused by buckwheat, Case 6 caused by carrots, the test indicates a great deal. If the suspected substance is ingested, as were carrots in Case 6 and urticaria reappears, the evidence obtained by the tests seems significant. Every one is familiar with instances in which simple foods cause urticaria and on numerous occasions their pathogenicity has been proved by cutaneous tests, notably in buckwheat poisoning and in egg urticaria.

2. *Inconsistencies.*—Inconsistencies depend on mechanical data, as mentioned above, ignorance of foods ingested, as people reacting to substances they deny having eaten, and perhaps, congenital variations making them susceptible or spontaneously sensitized (III, 2, 3 and 8). Perhaps the most important consideration, however, is involved in questions of specificity and group reactions (II, 1 and 2, and III, 10).

VI. PRACTICAL VALUE OF THE TESTS

Other things being equal, and with an understanding of the possible limitations and variations in the test, a positive test, subject to conditions analyzed above, and exceptions to be indicated below, signifies sensitization to a given protein.

1. *Indications of Specificity.*—As Longcope states, and as the work of Schloss and Smith indicates, the tests may be absolutely specific. In serum sickness, however, Longcope found that the test disappeared after the onset of the disease. Unquestionably, a specific test is

obtainable, as Cases 1, 2 and particularly 3, and 6 of our series indicate. In Cases 2, 3 and 6, removal of the indicated articles determined the end of the disease. In Case 4, a large number of foods was implicated, and these foods had been included in diet especially prescribed for the patient's condition. Her first improvement dated from the elimination of the prescribed articles and the substitution of a diet consisting of substances to which she had reacted negatively. The same is true of Case 9, in which tomatoes caused the outbreak. This patient was not observed long enough to have ruled out recurrence.

On the other hand, removing the suspected substances sometimes is without result. In Cases 10 and 12 there was recurrence after improvement. Of the remaining seven cases, Case 1 was not due to food sensitization, but to vegetable substance in cosmetics. The patient recovered when he discontinued the use of these cosmetics. The patients in Cases 7 and 11 were not tested. The remaining four showed features already mentioned, or to be mentioned, but on the whole prejudicial to the value of the tests. Eight of the twelve cases tested, however, support its value.

2. Limitations of the Test.—The limitations of the test are perhaps better described as the limitations of our understanding of the test. Nevertheless, we may justifiably conclude that the tests themselves still present some inherent imperfections. In the first place, the proteins used are not those we eat. On the other hand, what we eat is by no means what we absorb, or what sensitizes, but must be some hydrolyzed or cleavage product resulting from digestion. We know, however, that these derivatives inter-react specifically with their parent. We further know, as nearly all our cases reveal, that there is usually sensitization to more than a single substance. The explanation of this has already appeared. In short, it is a matter of group reactions and factors inherent in the concept of split proteins. Moreover, alimentary sensitization depends on anatomic or functional disturbances, and sensitization may continue through introducing chemically like though biologically unlike substances when we attempt to modify diet with regard to suspected foods. In such an eventuality, the disease would necessarily continue. Thus no patient, until more is known of the actual facts, should be given a suspected food, without being observed for attacks of urticaria, and no cure can be expected without adequate treatment of the gastro-intestinal tract, or the latter will continue its rôle as portal of entry.

Some forms of urticaria may not be anaphylactic. This seems unlikely, although possible, as Case 5 shows. A weakly positive response to salmon was elicited in this patient, but ingestion of the suspected substance provoked no attacks. All other food substances gave negative reactions. It is probable that we did not find the right protein in this case.

3. *Value of the Tests.*—The value of the tests may be summed up as follows: Positive reactions indicate sensitization to a protein or certain proteins, as in Cases 2, 3, 4, 6, 9, 10, 11 and 14. In seven of these, the removal from the diet of the single, or the most strikingly reactive of several substances, determined a cure, and in two more, improvement, albeit with recurrence. The significance of negative tests was summed up in the last paragraph of the section preceding this.

4. *Clinical Application of the Tests.*—The limitations of the test are embraced in the newness of the method which requires improvement, in the fact that the urticarial skin is inherently irritable and may give false reactions, and in our ignorance of the clinical significance both of anaphylaxis in man and its demonstrability by local reactions. In addition to this, it requires time and perseverance on the part of both physician and patient, and a great spirit of cooperation on the part of the latter. No more than two dozen tests can be made at a sitting, and thus about seven visits are required, four to complete the series, and two or three more to corroborate the findings. But the method should be pursued, because it promises practical aid in diagnosis and therapy, as our cases show. We do not subscribe at all to Strickler's pessimism, for he worked with too few proteins to justify his condemnation of the procedure. Had it aided us less than it did, we should be loathe to relinquish the method until convinced of its worthlessness. We are convinced of precisely the opposite, and the faintest praise we can accord it is that it at least tends to elide guess work in explaining the cause of urticaria, and in treating the disease.

VII. CONCLUSIONS

1. Are urticaria and allied conditions, notably angioneurotic edema, anaphylactic manifestations? The answer is affirmative, with certain possible exceptions, and sensitization mainly occurs through an anatomically or functionally deranged intestine.

2. Do positive tests prove them to be anaphylactic? This question, too, is answered affirmatively. Sensitization can be demonstrated by local reactions. The qualifications have been discussed.

3. If not, what may their nature be? Possibly, but not probably, they may indicate susceptibility or idiosyncrasy (III, 3 and 4; IV, 3).

4. If not, what do the tests signify? They may indicate merely a tissue reactability required for response to any pathogenic agent, but this is unlikely, for no other diseases except bacterial ones, react in a manner suggesting allergy (IV, 3).

5. What is the practical value of the tests? The practical value of the tests is far reaching. First (V) positive tests indicate sensitization. Second (VI, 1), they show sensitization to certain definite proteins, either singly or in groups.

6. How are they to be clinically applied (VI, 4)? The suspected articles are to be removed from the diet. One by one they should be given to the patient. Those provoking recurrences should be permanently eliminated. Desensitization is to be practiced only as to important foods, and particularly in infants and children in whom the diet is necessarily restricted. No cures can be expected unless the abnormal digestive tract, which is the avenue of sensitization, is treated.

Certain other conclusions that cannot be incorporated in the answers to the six problems must be mentioned.

7. Of sixty-three positive reactions, thirty-seven were to vegetable, twenty-six to animal proteins.

8. Reactions to more than one protein occurred in eleven cases of twelve tested.

9. Reactions to both vegetable and animal proteins occurred in ten cases. In Case 3, however, only buckwheat was tried.

10. Suprarenal extract was of benefit in eight cases, not employed in five, and caused collapse in one.[43]

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43. In addition to the references already given, the following may be of interest:

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ABSTRACT OF DISCUSSION

ON PAPERS OF DRS. TOWLE AND HIGHMAN AND MICHAEL

DR. HARTZELL was much pleased by the conversation of the gentlemen who discussed protein sensitization. It was one not only of scientific and academic interest, but of extreme practical importance. Many of the so-called special discoveries and advances in medicine spread from centers like this out to the general practitioner and he did not always use them as they might be used, but abused them. He had recently seen a number of such instances, and within a few weeks had heard a pediatrist state that infantile eczema was nothing but an anaphylactic phenomenon. Dr. Hartzell did not believe this. He had seen for some time past infants and children from 10 to 12 years of age who did not get enough to eat, and their physicians told him they were afraid those children could not digest certain proteins. Dr. Hartzell believed all would agree that urticaria was in the main a phenomenon of anaphylaxis, but was it always so? All had heard of the classic case reported years ago by Hebra in which urticaria could be produced by passing a uterine sound. It was rather difficult to explain this on any theory of anaphylaxis. One of the gentlemen had stated that dermographism was frequently associated with this trouble. Two of the most pronounced examples of dermographism that Dr. Hartzell had seen were associated with pediculosis corporis. In a case seen recently with a most extraordinary dermographism, with the disappearance of the pediculosis the dermographism disappeared promptly.

To return to the question of eczema as an anaphylactic phenomena, one was back to the old question, what is eczema? Dr. Hartzell would not deny that certain types of dermatitis might resemble eczema, but he did not believe that eczema and chronic dermatitis, which we regard as eczema, were of anaphylactic origin.

DR. FORDYCE said one of the most striking examples of the so-called anaphylactic or anaphylactoid reaction to a foreign protein was the case of a man who could not eat shell fish. If he touched the fish with his fork and put the fork in his mouth he would immediately have an outbreak of generalized urticaria. He had repeated this test many times and always with the same result. A young woman developed an outbreak of erythema iris after eating lobster. After three months she ventured again to eat lobster and had an outbreak of bullous erythema involving her face, arms and thighs.

Dr. Fordyce thought attention should be called to the sensitization of the skin that sometimes followed repeated injections of arsphenamin. He had a patient who was treated over three years ago and who developed after his fourth injection of arsphenamin a generalized exfoliative dermatitis. Three years after the dermatitis he was given a small injection of the drug, which was followed within twenty-four hours by an erythematous rash that progressively involved the entire body. His experience had taught him never to repeat the arsphenamin if the patient had previously developed an exfoliative dermatitis following its use. Sensitization to drugs was not alone confined to their internal administration. Analogous conditions have been seen after exposure to liquor formaldehydi. He had recently seen a generalized case of exfoliative dermatitis following the prolonged application of a hair dye which was chemically a paraphenylendiamin compound. This woman suffered for two months from the dermatitis and during part of this time she had an irregular rise of temperature sometimes as high as 103 degrees. She had a leukocytosis of 30,000

and an increase of eosinophils to 30 per cent. Dr. Fordyce desired to emphasize especially the skin allergy after the development of the generalized exfoliative dermatitis from arsenic.

Dr. Smith, apropos of Dr. Fordyce's remarks on sensitization to arsphenamin, recalled the case of a gentleman who was seen by Dr. White and a probable diagnosis of mycosis fungoides made. There were certain syphilitic manifestations and a positive Wassermann reaction; rather small doses of arsphenamin were given. Before this he had received a certain amount of roentgen-ray treatment for his supposed mycosis. Several months after receiving the arsphenamin, he was given Fowler's solution and became sensitized. He then disappeared for approximately two years and returned showing definite late manifestations of syphilis and received 0.3 gm. of arsphenamin. The fact that he had been sensitized to Fowler's solution three years before was overlooked. He promptly developed a severe arsphenamin dermatitis especially over the areas treated before with the roentgen ray. Dr. Smith thought it was surprising that this sensitization had persisted for such a long time.

Dr. Howard Fox spoke of his work in conjunction with Dr. J. Edgar Fisher during the past six months with the protein skin tests. In fifteen cases (other than eczema) of urticaria, erythema multiforme, angioneurotic edema and a few other skin diseases, the practical results had been unsatisfactory. Their experience in sixty cases of adult eczema had also been disappointing. The cutaneous tests with commercial proteins had been used, following the technic of Walker of Boston. Of the sixty cases, nineteen gave positive reactions to one or more proteins. It was rather surprising to find that most of these reactions were given by the proteins of vegetables and cereals.

As most of the patients were private patients it was not feasible, as a rule, to withhold all treatment for several weeks to watch the effect of a modified diet. A striking result occurred in one case in which no treatment was given and merely the reacting foods eliminated from the diet. This patient gave a strong reaction to cabbage and several other foods. After omitting these articles from his diet, his eruption of eight years' duration cleared up for the most part in a short time. It later recurred when, on request, he again ate cabbage. In some cases the results were contradictory. Patients reacted to certain foods, but failed to improve when they were removed from the diet. Dr. Fox said that he and Dr. Fisher finally concluded that the skin tests might ultimately prove of value in a small number of cases of adult eczema.

Dr. Schamberg said that an attempt had been made by certain students of this subject to clarify the atmosphere by assuming two different processes, one an anaphylaxis and the other allergy or hypersensitiveness to nonprotein substances. How much scientific basis there was for this differentiation, it was impossible to say. As Dr. Highman said, certain drugs combine with proteins of the blood and then acquire the properties of proteins; especially was this so with arsphenamin. As soon as it is introduced into the blood it combines with the globulin or protein of the serum. There was a strong parallelism between dermatitis venenata and pollen catarrhs. Many persons suffer with plant poisoning, especially ivy poison, a much greater percentage perhaps than suffer with hay fever. It is impossible to speak with positiveness concerning the nature of the substance that produced the ivy poisons. We know that there is a great variety of antibodies which may be produced in response to the introduction of various antigens into the system. Some are doubtless of the nature of antitoxins. There are two types of cutaneous reactions, one exemplified in the

von Pirquet test and the other in the Schick test. A positive von Pirquet reaction means that a specific antibody in the body has reacted with the antigen injected into the skin. With the Schick test it is to determine whether the subject has natural diphtheria antibodies in his body. A positive reaction indicates that there is no antitoxin in the blood to neutralize the injected toxin, whereas a positive reaction with the von Pirquet test means that there are antibodies in the blood. It must be remembered that a positive result in the two tests lead to quite opposite deductions.

As to the practical value of cutaneous food tests, in his experience he had found that in a few instances they have given information of the greatest possible value. In the majority of instances they have proved great disappointments. The type of local reaction varies greatly according to the method employed. If the abrasive method is used the resultant reaction is a wheal, which develops in fifteen minutes, whereas if the intradermal puncture is used the resulting reaction is a nodule, which appears within twenty-four hours.

Dr. Wile said that he would like to inject a little question of doubt into much that had been said in the previous discussion. He thought there had been a loose use of the terms "anaphylaxis" and "sensitization." As he understood anaphylaxis it was not only individual inability to metabolize certain substances, but the term included the ability to transfer similar reactions to laboratory animals passively, by injection of the offending substance and the patient's serum.

Dr. Wile had had the opportunity of discussing with Dr. Schloss, at great length, some years ago the classic case of Dr. Schloss referred to. It was only after the latter was able to produce passive anaphylaxis in laboratory animals, with ovomucoid, the offending substance in egg white, and the patient's serum, that Schloss was satisfied that he had proved out anaphylaxis. The mere percutaneous tests on the skin with various protein substances that might react positively was to his mind not even presumptive evidence that such substances were necessarily anaphylactic to the person. They might suggest occasionally accurately a hypersusceptibility, but, as Dr. Engman had shown, a positive test could occur with certain substances in persons who did not and had never shown idiosyncrasy to such substance.

Dr. Hazen thought it was impossible to study this phenomenon without considering the vegetative nervous system. He remembered a child who had urticaria and this was combined in many instances with bronchial stenosis and asthma. The history, according to the child's mother, was that after riding behind a horse, and after eating eggs and chicken these attacks would come on. Dr. Hazen saw the child in one attack and found that he had a dermatitis, a true bronchial asthma, a true pyloric stenosis, a spastic colon and classic eye changes, and on examination he found that he reacted to the skin tests of horse dandruff, egg albumin and chicken. These had produced an effect on the vagus nerves and the things found clinically were due to vagotonia. At the same time Dr. Hazen did not think one was justified in thinking all these were due to allergy or hypersusceptibility.

A well-known man in Washington had three children, one of whom Dr. Hazen saw a number of years ago because of a dermatitis. Associated with this was pyloric stenosis, bronchial asthma and a spastic colon. A few days before another boy put a dog on him and the father came along and scolded the boy. Within a few minutes the boy had developed all the signs of a vagotonia. In the same family other children developed attacks absolutely similar in every respect, and these attacks could be controlled promptly by the

use of atropin. In other words, some of the attacks unquestionably are due to a vagus irritation and this is not always due to a hypersusceptibility or an allergy; in some instances they are due to marked mental irritation. This would explain some of the cases of urticaria when a patient was in a doctor's office, and when a uterine sound was passed. In a case of scabies it was possible that the absorption of the parasite would explain it, due to absorption of the protein, but not necessarily through the food tract.

Dr. Grindon thought it was possible that urticaria might be due to two causes, one anaphylactic and the other nervous in origin. To the latter group probably belonged the case of the girl mentioned by Leloir who developed urticaria whenever she was kissed. While true anaphylaxis differed from sensitization to nonprotein drugs, yet there was a certain relationship between these phenomena. If a person was subject to the one he was probably subject to the other. In a family under his observation for a number of years, a certain lady had urticaria every time she took quinin. A sister was similarly affected. She enjoyed most excellent health except that she was subject to hay fever. On one occasion Dunbar's pollantin, which was a horse serum, was used with considerable relief of the symptoms. Some years later during an attack, a drop was placed in each eye sac and a drop in each nostril. Within a few seconds she became dyspneic, the conjunctivae swelled so that they protruded from the eye clefts and the cornea could be seen at the bottom of a cup. The symptoms were most alarming, but passed off within a few minutes. One of this lady's children was given an immunizing dose of diphtheria antitoxin. Three years later the same child ran a rusty nail into its foot and was given a dose of tetanus antitoxin. Within a short time it was enormously swollen, with the eyes closed tight, the hands and fingers much swollen, and the lips everted. That condition continued off and on for three weeks; it would entirely disappear and then return. After this had been going on for two weeks the child one day suddenly became dyspneic. Epinephrin was at once administered and within a few minutes the respiratory symptoms disappeared, although the skin symptoms continued. This family group showed undoubted sensitization, both to proteins and nonproteins. This might be explained by the protein combination of which Dr. Schamberg has spoken. Another of the children in this family was subject to urticaria from a wide variety of foods.

Dr. Carmichael recalled the case of the infant of a prominent physician in Cincinnati. The child was breast fed for six months without any trouble. At that time the mother became ill and the child was put on bottled milk in small amounts, when it promptly developed urticaria and convulsions and almost died. It was then suggested that goat's milk be substituted for cow's milk. This was procured and the child remained on this diet for eighteen months. It was then brought to Washington and at Dr. Carmichael's suggestion cow's milk was again tried. The child was given one teaspoonful of cow's milk and within a short time a severe urticaria resulted. The child had been tested and now the only positive reactions were for cocoa and grape juice. The child could take cocoa and grape juice.

Dr. Varney thought that desensitization, as the term was being used in the discussion, was the removal of the specific food or sensitizing substance rather than what he understood as desensitization. To desensitize a person would be to render him able to assimilate that article of food without symptoms of sensitization. Infantile eczema probably presents the most definite sensitization picture of any dermatosis. This particular form of dermatitis of

infantile eczema is fast being taken from the dermatologist by the pediatrician, largely because of our percentage of failures through, probably, lack of definite methods of determining the specific food or foods that cause the trouble.

Dr. Varney had been interested in attempts at desensitizing infants with chronic eczema of the face by administering small rectal injecions of milk every two or three days. The effect, clinically, within twenty-four hours is first a marked aggravation of the eczema, and then a prompt improvement in about 50 per cent. of the cases.

Dr. Engman said that what he meant by desensitization was the hypodermic injection of extremely small quantities of the offending protein, so that the patient could afterward use that article.

Dr. Hartzell asked whether the gentleman who referred to a dermatitis following arsphenamin thought the dermatitis was evidence of sensitization. Was such a dermatitis never the result of arsenical poisoning?

Dr. Fordyce was of the opinion that the case in which the eruption occurred after three years was due to drug sensitization.

Dr. Stokes had a way of suspecting an external factor in connection with eczema. If the patient started from home with a dermatitis and was nearly well when he arrived at Rochester they studied his environment. An interesting example of this was the case of a man from Tennessee who arrived in pretty bad shape but promptly recovered. He then went home and relapsed. It was found that the dermatitis was due to the ground bone mixture he fed his chickens. He got rid of the dermatitis by getting rid of this brand of chicken food.

Dr. Stokes wished to have Dr. Highman explain the observation of which he thought there were two recorded cases, in which raw egg white caused symptoms, whereas boiled eggs did not. Dr. Stoke's eldest son was an example of this. On the first occasion on receiving a spoonful of egg nog he immediately became cyanotic and greatly swollen, and had alarming symptoms. Since that time he had twice been the victim of raw egg white anaphylaxis. The second time was when some of the nurses went up to his house and decided that the boy had a cowlick which was not becoming and applied egg white in an attempt to improve his appearance. The boy at once developed the most alarming symptoms, a hurry call was sent to his father and when he reached home he found the boy cyanotic, the face tremendously swollen with the lower lip hanging down on the chin and giant wheals over the forehead and in the scalp. This boy could eat hard boiled eggs all the time and have no trouble, but if they were soft boiled he had a prompt response in the form of urticaria.

Dr. Stokes thought the work of Bruno Bloch was interesting in that he reported the transplanting of skin hypersensitive to trichophyton to the varicose ulcer of a patient who was not sensitive. It was found that even after the skin continued to grow on this foreign soil it still retained its sensitiveness to trichophyton.

Dr. Schamberg's mention of a tendency to distinguish between allergy and anaphylaxis reminded him that there was evidence that hypersensitiveness of the skin was not necessarily associated with systemic hypersensitiveness and that accordingly the findings in cutaneous tests could not be interpreted too literally or specifically in regard to the body at large. It was possible to demonstrate that *Spirochaeta pallida* had nothing to do with the positiveness of the luetin test and that the allergy of late syphilis might be imitated in a nonsyphilitic merely by injecting into his skin emulsions of his own skin.

Some recent experimental work by Meyers and his collaborators had tended to show that systemic egg white anaphylaxis in guinea-pigs is not necessarily associated with cutaneous hypersensitiveness to egg white.

Dr. Pusey thought that in this Friday night experience meeting the members had, in their engrossment in giving their own experiences, failed to comment sufficiently on the excellent character of the two papers that opened the discussion, for which he thought the Association was much indebted to the writers. They not only covered the subjects in an exhaustive way, but temperately and wisely. They had, in fact, epitomized all sound information on the subject up to the present. Dr. Pusey gathered that the experiences of most of the gentlemen agreed with his; that specific sensitization tests had not thus far proved of as great practical value as we had hoped they would. He, however, felt that the subject was founded on sound premises and that small as were the practical results at present, there were possibilities of much usefulness in the future.

Dr. Towle (closing) thought the situation could be summed up very well in a phrase—"He damned it with faint praise." He had found great difficulty in writing his paper, in trying to put it in positive terms rather than indefinite terms, and the discussion had corroborated his difficulties.

Dr. Hazen spoke of the vegetative nervous system and tried to draw a sharp line where no sharp line was possible.

Dr. Schamberg spoke of the close relationship between a hypersensitive skin and anaphylaxis. Where does the one begin and the other end? That was the difficulty—they had not stopped to consider what was doing. This was not to deny that anaphylaxis did not exist, but the other also existed and always had. A good example of similar conflict of opinion is found in hysteria. Can it of itself cause actual physical signs? Some authorities say that it can and others that it cannot. A rather illuminating act is that of a Boston man specializing in food testing who has abandoned preparing a special specific substance and has adopted the practice of preparing a single immunizing substance which he gives alike to all patients, and gets equally good results. He labeled it "341" and all the patients got it.

As to the intestinal tract, it is well known that the intestinal tract becomes more permeable in the presence of pathologic conditions. Putrefaction favors congestion, congestion interferes with the normal function of the mucosa, and that favors absorption. The only question that remains to be settled is why patient "A" becomes sensitized to pork and patient "B" refuses to be sensitized. It is evident that there is a foundation somewhere and the profession must find that foundation and then determine what building should be erected on that foundation. The fact should be accepted that physicians know the pros and cons but are utterly ignorant of what goes on between the two.

Dr. Highman (closing) said there was so much to be said that had been inspired by the adequate discussion that it was hard to know where to begin.

As to Dr. Wile's theory, he participated with him in his doubts as to the relationship of anaphylaxis and sensitization in a great many instances, and thought further experimentation was necessary. One experiment by Bruck was significant. He had a patient who was sensitized to pork, so he sensitized a guinea-pig to pork and then injected some of the patient's serum into the guinea-pig and produced anaphylactic shock. That showed how closely in this patient the entire complex held together.

As to the question of Dr. Stokes in regard to the egg white, he thought he could explain that. Anaphylatoxin was destroyed at 100 degrees, which was required to boil an egg hard. He did not know why the eggs would affect some children when they were boiled and some when they were raw, but so far as he was familiar with the literature, hard boiled eggs were not assumed to produce anaphylactic shock.

The question brought up in connection with the relation of hypersusceptibility to anaphylaxis was, Dr. Highman thought, a matter of academic distinction. He believed one should use the term anaphylaxis in a restricted sense as applying solely to protein poisons, and that the types of irritability of the skin seen in response to mercuric chlorid or rhus did represent something in another category. As a matter of fact, even these conditions have the elements of the cutaneous sensitization, because people who were sensitive to ivy or mercuric chlorid or any of the other substances, obviously responded in a manner somewhat similar to what occurred in some forms of food poisoning. The relation of anaphylaxis and the relation of cutaneous sensitization to anaphylaxis were not clearly understood, and, finally, the relation of cutaneous tests to the whole affair was not clearly understood, so we were venturing in a field that as yet had scarcely been explored. For this reason all scientific notions must still necessarily be vague. The whole thing must be considered with a sort of optimistic skepticism. In a series of twelve cases, which he analyzed, eight were illuminated by the test both as to the etiology and therapy. In the next series of twelve this might be reversed. Twelve swallows did not make a summer and twelve cases in a series did not constitute a thesis. We must approach the subject with an open mind. If it proved of value the value would be great, and if it had no value there was certainly no harm in traveling this uncharted sea.

Dr. Engman (closing) said that in egg white sensitization, bread toast could frequently be used, as could hard boiled eggs, when egg white could not be used. He thought words rather than the fundamental principles were being discussed. Was there something in which they could take the offending article which might enter the system and come in contact with the skin? There was, and if not all cases of urticaria were due to it, or all cases of eczema, some undoubtedly were. As men who limit their work to the realm of skin diseases, Dr. Engman felt that dermatologists should thoroughly investigate the subject as others were doing in other branches. The test was very delicate and had to be performed with great care, and it did not always have the same effect on a patient. Findings might be obtained at one time and none the next, and the offending element might not be recognized.

Dr. Markley (closing) said that it was well known that the epidermal products of certain animals may cause general sensitization with the production of asthma or hay fever as well as skin manifestations; under such circumstances the nature of the disorder is usually recognized, but if the skin alone is sensitized it presents a more difficult problem. If the skin is sensitized in local areas the skin test will, of course, be positive in these areas but negative in unsensitized areas, the result being therefore obscure unless multiple tests be made, as pointed out.

LYMPHOGRANULOMATOSIS OF THE SKIN IN HODGKIN'S DISEASE*

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The cutaneous manifestations of Hodgkin's disease may in general be divided into two classes. The first of these includes a group of dermatoses not characteristic of Hodgkin's disease either clinically or histologically. In this class should be mentioned generalized prurigo-like eruptions, pruritus, urticarial, hemorrhagic and bullous eruptions, pigmenation and universal exfoliative erythrodermias. In addition, certain disturbances of nutrition, such as alopecia areata, have been noted. Whether these manifestations are due to the toxic action of the (supposed) infectious agent in Hodgkin's disease, it is not my purpose to discuss. That the prurigo-like eruptions are not characteristic of this disease has been shown by microscopic examinations by Bowen [1] and others. In a woman with typical Hodgkin's disease, Bowen noted prurigo-like lesions on the leg, one of which was examined histologically. He wrote, "It seems to me most rational to regard them as akin to the nodules of true prurigo, as their clinical aspect and histologic structure agree completely with the latter." The second class of cutaneous manifestations of Hodgkin's disease is represented by tumor-like infiltrations with typical histologic structure.

The frequency of the cutaneous manifestations in Hodgkin's disease has been discussed by Cole [2] in a recent paper. He quotes the opinion of Ziegler that "one fourth of all cases of Hodgkin's disease at some time or another in the course of their trouble showed evidence of skin involvement." He also mentions that Westphal found cutaneous lesions in 15 per cent. of his cases. Though at first inclined to think that these figures were rather high, he came to the conclusion, after two years of careful observation of such cases, that they were probably correct.

Manifestations of the skin analogous to those of Hodgkin's disease are seen in the leukemias, particularly of the lymphatic type. Those analogous to the first class (above mentioned prurigo-like

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* From the United States Public Health Service.

* Read at the Forty-Third Annual Meeting of the American Dermatological Association, Asheville, N. C., April, 1920.

1. Bowen, J. T.: Mycosis Fungoides and Sarcomatosis, J. Cutan. Dis. **15**: 65, 1897.

2. Cole, H. N.: The Cutaneous Manifestations of Hodgkin's Disease: Lymphogranulomatosis, J. A. M. A. **69**:341 (Aug. 4) 1917.

eruptions, urticaria, etc.) have been spoken of by Audry [3] as leukemids; by Arndt [4] as lymphadenids in contrast to the characteristic infiltration which he calls lymphadenosis.

The case which forms the basis of this communication I hope to show was one of Hodgkin's disease, presenting tumor-like infiltrations of the skin, that is, lesions of the second class mentioned above. The patient was in charge of the U. S. Public Health Service, to whom I am indebted for the privilege of making this report. Every possible help in studying this case has been rendered and the hospital records (Polyclinic Hospital) have been frequently quoted. The patient has been under the immediate care of Dr. Elias A. Reed, chief of the Medical Service, to whom I am especially indebted for assistance.

REPORT OF A CASE

History.—Feb. 5, 1920. The patient, A. H. A., was a man 30 years of age, born in the United States, originally a grocer's clerk. His parents and three sisters were living and healthy. There was no family history of tuberculosis, cancer or any other disease similar to the present one. As a child he had suffered from measles, mumps and diphtheria. He served in the U. S. Marine Corps from 1909 to 1913 and while in Panama, in 1911, contracted malaria. He served as an enlisted man in the United States Army from February, 1914, to March, 1919. He was operated on for hernia in 1917. During the World War he had about ten months' service in France, during which time he suffered from influenza, complicated by pneumonia. He denied venereal disease. His habits were moderate as to alcohol and tobacco. His appetite was good, bowels irregular. He gave no history of rheumatism or attacks of sore throat.

The present illness began in January, 1919, the patient noticing small hard lumps in the neck and scalp. In December, 1919, he was examined by a private physician, who recognized similar lumps in the groin and axillae and recommended the removal of one of them for diagnostic purposes. The result of this examination is given below. A clinical diagnosis of Hodgkin's disease was made at that time. Since May, 1919, the patient had complained of dyspnea on exertion, substernal pressure and a sensation of weight in the abdomen. He has had no dysphagia, night sweats, diarrhea or loss of weight.

Physical Examination.—The patient was a man of medium height, weighing 155 pounds, well nourished and of ruddy complexion. Vision and eyegrounds were normal. The nose showed a deviated septum, enlarged turbinates and hypertrophic rhinitis. The tonsils were slightly enlarged. The ears were normal with the exception of impacted cerumen. Five teeth were missing, four were capped. The lungs were resonant throughout, harsh breathing being heard over the bronchi. The heart was regular as to force and rhythm with no murmurs or thrills. The second pulmonic sound was accentuated. The abdomen was soft, the muscles well developed The spleen could be felt 1 inch below

3. Audry, C.: Sur les leucémides, Ann. de Dermat. et de Syph. **3**:310, 1902.

4. Arndt, G.: Zur Kenntnis der leukämischen und aleukämischen Lymphadenose (lymphatischen Leukämie und lymphatischen Pseudoleukämie) der Haut mit besonderer Berücksichtigung der klinischen und histologischen Diagnose und Differentialdiagnose, Dermat. Ztschr. **18**:1, 1911.

the costal margin, the edge being hard. The liver was felt at the costal border. The kidneys could not be felt. There was considerable tenderness on pressure in the right hypochondriac region. The bones, joints and muscles of the extremities were apparently normal. The reflexes were exaggerated. The blood pressure was systolic 120, diastolic 80. The urine was normal. The Wassermann reaction was negative. Roentgen-ray examination of the chest showed "apices hazy, pulmonary fields clear; mediastinum within normal limits; slight hilus enlargement but no evidence of adenopathy."

Examination of the blood on Feb. 12, 1920, showed: hemoglobin, 75 per cent.; red cells, 5,664,000; white cells, 6,600. Differential count: polymorphonuclears, 68; small mononuclears, 27; large mononuclears, 2; eosinophils, 1; basophils, 0; transitionals, 2.

During the two months while the patient was treated at the Polyclinic Hospital (U. S. Public Health Service) he had had a rise of temperature on two occasions (100 and 101 F.) and for a short time his temperature was subnormal.

Examination of Lymphatic Glands.—This showed a moderate enlargement of the lateral and posterior cervical, submaxillary and inguinal groups. They were firm and painless, the overlying skin being normal in appearance and not adherent. The largest gland, about the size of a horse chestnut, was in the posterior cervical region. These were later treated with the roentgen ray and reduced in size. A histologic examination of an excised cervical gland was made in the fall of 1918 by Dr. Warren B. Stone, pathologist of the Ellis Hospital in Schenectady. He reported: "The gland was 0.5 cm. in diameter and exhibited an hyperplasia of lymphoid tissue, together with numerous epithelioid cells and eosinophils. I found also a few giant cells of the Dorothy Reed type and from these findings made a diagnosis of Hodgkin's disease."

Cutaneous Lesions.—These were confined to the face and scalp. They involved practically all of the scalp except the occipital region, half of the right side of the forehead and both temporal regions. They consisted of diffuse, painless, lumpy infiltrations involving the skin and subcutaneous tissue. The surface of the lesions was dry, shiny and of a dull purplish color. There was no evidence of scratching, although the patient complained of occasional slight itching. The most prominent of the tumors was about 2 inches in diameter, elevated about a quarter of an inch above the scalp. On the right side of the forehead was a large, infiltrated, slightly elevated patch, about 3 inches in length, fading from the surrounding normal skin. There were also smaller patches in the temporal regions. There was considerable whitish, branny desquamation scattered over the vertex. There were a few superficial scaly patches on the cheeks. In the midscapular region was a group of a dozen cutaneous nodules of color and consistency similar to those on the scalp. The largest of these was distinctly elevated and about the size of a dime. It was in the region of these nodules that the patient had received about two dozen subcutaneous injections about eight months previously.

HISTOLOGIC EXAMINATION OF THE SKIN

A piece of tissue from the anterior portion of the scalp was excised under local anesthesia on February 17 for histologic examination. This was made by Dr. Walter J. Highman who reported:

Low power (B. & L. eye piece 10, objective 16 mm.); hematoxylin and eosin stain. The epidermis shows no noteworthy abnormalities. There is a diffuse

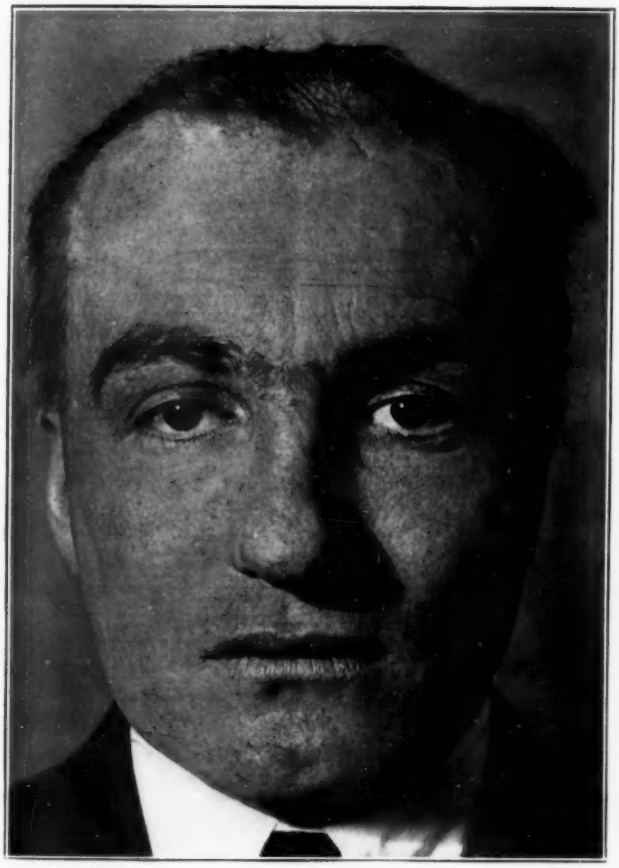

Fig. 1.—Lymphogranulomatosis of the skin showing cutaneous tumor-like infiltrations.

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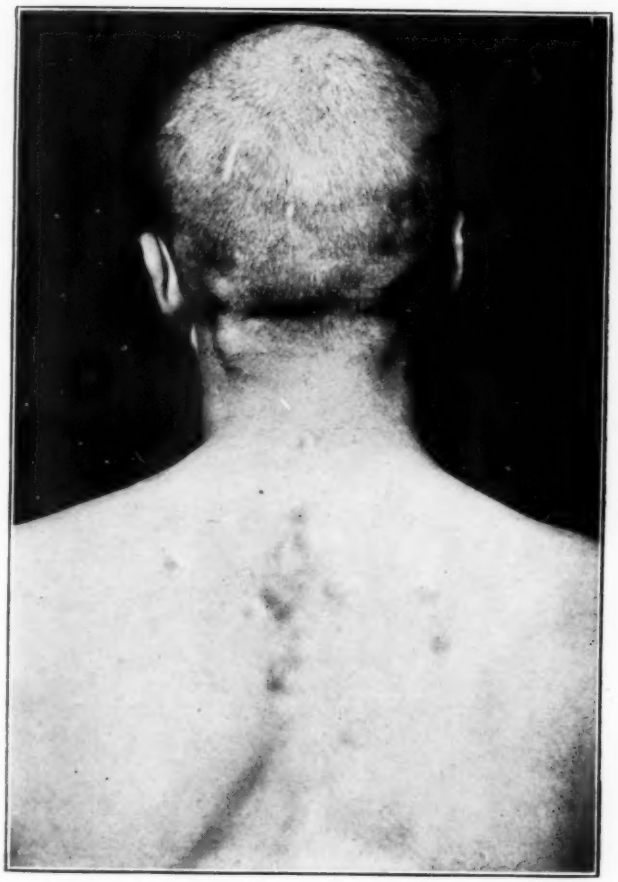

Fig. 2.—Lymphogranulomatosis of the skin and glandular enlargements.

infiltration in the corium from the subpapillary plexus to the utmost depths and although the connective tissue has been disturbed and to a large degree absorbed, the hair content is normal and the arrectores are present.

High power (B. & L. eye piece 10, objective 4 mm.). Under higher magnification the infiltration can roughly be divided into two types, a series of masses, darkly staining uniform cells which are prevailingly perivascular in position, or at least intimately related to the vessels. These groups of cells lie as relatively circumscribed islands in their diffuser, somewhat denser general infiltration. For purposes of convenience let them be called islands and general infiltrations. The island infiltrations consist entirely of cells resembling small lymphocytes as found in the blood, in that they possess a large circular dark nucleus, surrounded by a narrow zone of cytoplasm or apparently none at all. The cells of the general infiltration consist about evenly of the small round type, small and large mononuclear types, with few epithelioid cells and a fairly large number of dividing binucleated cells. There are no plasma cells and no Langhans cells, but mixed with the infiltrations are numerous fibroblasts and an occasional mature connective tissue cell (fixed cells). From time to time, but not in large numbers, an eosinophil cell is observed within the capillaries.

In certain areas there is a great deal of cell detritus, indicating a distinct tendency to necrobiosis. Many uninucleated, large irregular cells not admitting of routine classification are seen. These are probably the mononuclear variety described by Dorothy Reed and Sternberg. Numerous large bodies with three to nine vacuolated, large or small, elongated or rounded nuclei are observed. The size of the cells and their nuclear contents depend on the segment of the cell cut. These suggest Dorothy Reed bodies. The collagen immediately below the epidermis is well preserved throughout the infiltration and is represented by fragments that take the stain relatively faintly. The elastic tissue is preserved in the subpapillary areas; elsewhere it has undergone changes parallel to those of the collagen. The vessels are not increased in number, although the small capillaries throughout are somewhat dilated.

The arterioles are slightly swollen as to all their coats, but show no great thickening as in syphilis. Occasionally the lumen is nearly occluded by edematous endothelial cells. The veins are moderately dilated but otherwise undisturbed. The lymphatics of all types are dilated and engrossed with lymphatic cells already alluded to.

Summary.—The infiltration is lymphogranulomatous and can be only mycosis, or pseudoleukemia (Hodgkin's disease). In mycosis we should expect to find chorioplaques and mitoses in great abundance. In leukemia there would be a greater uniformity of the cells. The presence of Dorothy Reed bodies favors the diagnosis of Hodgkin's disease. If Hodgkin's disease causes skin granuloma containing Dorothy Reed bodies, this must be Hodgkin's disease.

Course and Treatment.—March 8: Roentgen-ray treatment of scalp and forehead was given. Two areas were treated with 1 Holzknecht unit (skin distance) filtered through 3 mm. of aluminum.

March 12: White blood cell count was 7,800; differential count: polymorphonuclears 81, small mononuclears 14, large mononuclears 1, transitionals 1, eosinophils 2, basophils 1.

March 13: Photographs were taken of the head and back.

March 29: Roentgen-ray examination of the chest showed enlarged glands of the left hilus, questionably of the right. No other pathologic condition was observed. The apexes of the lungs appeared normal.

Spinal fluid examination showed 10 cells (mononuclears), the presence of sugar, a faint ring of albumin and a negative Wassermann reaction. Rate of flow was 60 drops per minute. Blood examination revealed: hemoglobin 75 per cent., red cells 4,640,000, white cells 8,600. The differential count was: polymorphonuclears 79, small mononuclears 19, large mononuclears 1, transitionals 0, eosinophils 1, basophils 0. No abnormal cells were present. Blood culture was negative. The blood Wassermann reaction was negative. The Widal reaction was negative and no plasmodia were present.

April 3: Von Pirquet's test was negative.

April 6: Roentgen-ray treatment of the scalp was given. Two areas were rayed with 1 Holzknecht unit (skin distance) filtered through 3 mm. aluminum

April 16: The patient had lost 15 pounds in the past three months.

Histologic examination of the gland: A gland excised from the axilla on March 30 was examined by Dr. Walter J. Highman, who reported that it "showed hyperplasia, the cells being mainly lymphatic. Numerous examples of both forms of the Dorothy Reed bodies were observed, but there were no eosinophils."

OTHER CASES REPORTED

The cases of true Hodgkin's disease of the skin (in the sense of a lymphogranuloma) that have been described in the literature are few in number. Grosz,[5] in 1906, working in Paltauf's laboratory, published his classic paper "On a Hitherto Undescribed Disease of the Skin (Lymphogranulomatosis Cutis)." Since then similar cases have been reported, some of them in great detail, by Hecht,[6] Neumann and Pick,[7] Nobl,[8] Bruusgaard,[9] Ziegler,[10] Arndt,[11] Cole and Trimble.[12]

Alderson's [13] patient, with lesions on the legs resembling gummas, showed the presence microscopically of a lymphogranuloma with numerous eosinophils. Ophuls, who made the histologic examination, said "On account of the numerous eosinophils, the large lymphatic cells and the whole character of the lesions, which resembles the

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5. Grosz, S.: Ueber eine bisher nicht beschriebene Hauterkrankung (Lymphogranulomatosis Cutis), Beitr. z. Path. Anat. (Ziegler) **39**:405, 1906.

6. Hecht, H.: Ueber lymphogranuloma, Arch. f. Dermat. u. Syph. **98**:107, 1909.

7. Neumann and Pick: Lymphogranulomatosis Cutis, Deutsch. med. Wchnschr. **35**:2033, 1909.

8. Nobl, G.: Lymphogranulomatosis Cutis, Wien. klin. Wchnschr. **24**:148, 1911. Ibid.: Lymphogranuloma papulosum disseminatum, Arch. f. Dermat. u. Syph. **110**:487, 1911.

9. Bruusgaard, E.: Ueber Hauteruptionen bei der myeloiden Leukämie und der malignen Granulomatose, Arch. f. Dermat. u. Syph. **106**:105, 1911.

10. Ziegler, K.: Die Hodgkinische Krankheit, Jena, 1911.

11. Arndt, G.: Beitrag zur Kenntnis der Lymphogranulomatose der Haut, Virchows Arch. f. path. Anat. **209**:432, 1912.

12. Trimble, W. B.: Pseudoleukemia Cutis (Hodgkin's Disease), J. Cutan. Dis. **37**:336, 1919.

13. Alderson, H. E.: Cutaneous Manifestations in Hodgkin's Disease, J. Cutan Dis. **35**:481, 1917.

tissue changes in Hodgkin's disease and certain types of lymphosarcoma, the most likely diagnosis to me seems to be Hodgkin's disease—metastatic of leg." The case was not a classic one, however, as there were no "giant cells" and as the lesions underwent necrosis. They did, however, respond favorably to the roentgen ray, a therapeutic agent that is known to have a marked effect on the lymphatic glands and cutaneous tumors of the leukemic group of diseases.

Trimble's patient was presented before the Section of Dermatology and Syphilis of the New York Academy of Medicine. As the report of this case in the transactions of the Section was very meager, Dr. Trimble has kindly given me additional information (personal communication) which shows this undoubtedly to be one of lymphogranulomatosis cutis. The patient was a man, 40 years of age, who was suffering from Hodgkin's disease as proved by histologic examination of an excised gland. There were cutaneous lesions on the side of the neck that suggested lupus vulgaris, though on close observation, no apple-jelly nodules were seen. A histologic section of an excised portion of the skin was made and the following condition found by Dr. Alexander Fraser: "In the corium and subcutis are foci composed of lymphocytes, epithelioid cells with a fair number of large multinucleated cells, which are usually regarded as characteristic of Hodgkin's disease. These cells are larger than the epithelioid cells and may have one or several nuclei, which are placed close to each other. The nuclear membrane is distinct and the nuclear chromatin sparse but the nucleoli stain deeply."

In the older literature some cases, as Arndt says, have been described under other titles, which he thinks should be considered in the class of lymphogranulomas. He specifically mentions the case of von Notthaft.[14] Other cases reported under the name of pseudoleukemia, Hodgkin's disease, etc., were not examples of the disease in the sense described later in this paper. These would include the cases of Pfeiffer,[15] Wende,[16] and Arning and Hensel.[17] In the case of Arning and Hensel the characteristic giant cells of lymphogranuloma are neither mentioned in the text nor are they present in the histologic drawings. It may be of interest to add that all, except one of the cases above quoted, occurred in males, following the well known

14. Von Notthafft, A.: Ein Fall von Pseudoleukämie, Beitr. z. Path. Anat. (Ziegler) **25**:309, 1899

15. Pfeiffer, T.: Ein Fall von Pseudoleukämie mit specifischer Erkrankung der Haut, Wien. klin. Wchnschr. **10**:549, 1897.

16. Wende, G. W.: A Case of Lymphatic Leukemia, Apparently Developing Out of Hodgkin's Disease, Am. J. M. Sc. **122**:836, 1901.

17. Arning, E., and Hensel, H.: Pseudoleucämia Cutis. Ein Fall von Pseudoleukämie mit Hauttumoren, Ikonographia Dermat., Pt. 4, p. 127, 1909.

preference of Hodgkin's disease for this sex. In Ziegler's 220 collected cases, more than half were males, while the statistics of Strobel and Hazen [18] showed 80 per cent. of frequency for males.

CLINICAL DIAGNOSIS IN THE AUTHOR'S CASE

Before discussing the cutaneous lesions of this case, it should first be shown that the patient was suffering from Hodgkin's disease, defining as well as possible the current conception of this affection. That there has been a great deal of confusion regarding the nature of Hodgkin's disease, first described in 1832, is evident from the many names that have been used to describe it. These include Hodgkin's disease (Wilks); progressive multiple lymph gland hypertrophy (Wunderlich); pseudoleukemia (Cohnheim); lymphosarcoma (Virchow); malignant lymphosarcoma (Langhans); desmoid carcinoma (Schultz); lymphogranulomatosis (Sternberg-Paltauf); lymphomatosis granulomatose (E. Fraenkel); malignant granuloma (Benda). The disease is defined by Longcope [19] as "an affection characterized by painless progressive enlargement, usually of several groups of lymph nodes and accompanied by a progressive anemia. Often the spleen and sometimes the liver are enlarged." In regard to the blood findings he says that there is "no constant or characteristic alteration." Other symptoms such as intermittent, remittent or at times continued fever, cachexia, night sweats, etc., briefly make up the clinical picture. Lymphatic leukemia is practically ruled out in my case by the negative blood findings, although it must be admitted that a lymphatic leukemia may for a time be aleukemic. Though Gulland and Goodall [20] scoff at the idea of an aleukemic leukemia, it is accepted by the majority of authorities. Naegeli [21] says the detection of a leukemia in this stage can generally, but unfortunately not always, be made from the presence of a marked relative lymphocytosis and the presence of pathologic types of leukocytes. The diagnostic value of these abnormal cells is also mentioned by Grawitz,[22] Ward,[23] and others.

Clinically my patient showed a painless, rather slight enlargement of most of the palpable lymphatic glands, a well-marked enlargement

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18. Strobel, E. R., and Hazen, H. H.: Mycosis Fungoides in the Negro, J. Cutan. Dis. **29**:147, 1911.

19. Longcope, W. T.: Hodgkin's Disease, Modern Medicine (Osler and McCrae), Philadelphia, Lea & Febiger, 1915.

20. Gulland, G. L., and Goodall, A.: The Blood: A Guide to Its Examination and to the Diagnosis and Treatment of Its Diseases, E. B. Treat, 1912.

21. Naegeli, O.: Blutkrankheiten und Blutdiagnostik, Leipzig, 1912.

22. Grawitz, E.: Klinische Pathologie des Blutes, Berlin, 1902.

23. Ward, G. R.: Clinical Haematology, Philadelphia, W. B. Saunders Company, 1914.

of the spleen, a mild anemia but otherwise normal blood picture, occasional fever, dyspnea and some asthenia. The clinical diagnosis of Hodgkin's disease was therefore highly probable. This was established by the microscopic examination of an excised gland.

PATHOLOGIC CONCEPTION OF HODGKIN'S DISEASE

It is necessary at this point to refer to the histologic findings, which at the present time are considered by many as characteristic of Hodgkin's disease. According to MacCallum [24] "the new tissue produced has a constant histologic character which is easy to distinguish from that seen in any other condition." Longcope [25] states that the first marked change in the smallest glands is an hyperplasia of the lymphoid cells. The reticular tissue becomes coarser and increased in amount and later almost all of its normal structure is lost. The reticulum then forms a coarse network enclosing cells of different types, narrow bands and young connective tissue dividing the glands into irregular lobules. In the reticular network are found large and small lymphocytes, plasma cells, polymorphonuclear and eosinophil leukocytes, epithelioid cells and finally the characteristic uninuclear and mononuclear giant cells. The connective tissue increases as the disease progresses. While the structures are very cellular at first, they ultimately change almost to fibrous tissue.

The peculiar giant cells mentioned were minutely described by Dorothy Reed [26] in 1902 and are often spoken of in this country as Dorothy Reed cells. Similar cells had been previously described by Sternberg,[27] and among German writers they have since borne his name. In speaking of Sternberg's article written in 1898, Reed says: "The histologic peculiarities of the growth from his descriptions and infiltrations agree closely with the changes met with in our series." Reed's description of the peculiar giant cells is in part as follows:

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24. MacCallum, W. G.: On the Pathological Anatomy of Lymphosarcoma and Its Status with Relation to Hodgkin's Disease, Bull. John Hopkins Hosp. **18**:337, 1907.

25. Longcope, W. T.: On the Pathological Histology of Hodgkin's Disease, with a Report of a Series of Cases, Bull. of Ayer Clin. Lab. of Penn. Hosp. **1**:4, 1903.

26. Reed, D. M.: On the Pathological Changes in Hodgkin's Disease, with Especial Reference to Its Relation to Tuberculosis, Johns Hopkins Hosp. Reports **10**:133, 1902.

27. Sternberg, C.: Ueber eine eigenartige unter dem Bilde der Pseudoleukämie, verlaufende Tuberkulose des lymphatischen Apparates, Ztschr. f. Heilk. **19**:21, 1898.

They vary from the size of two or three red blood corpuscles to cells twenty times this size. They usually lie free in the interstices of the tissues but we occasionally see them in the reticulum and with irregular protoplasmic processes. The nucleus is usually large in proportion to the size of the cell. It may be single or multiple. If single, it is usually round. Bean shaped and irregularly indented nuclei are common. If multiple, the nuclei may be arranged peripherally in the cell or heaped in the center. Eight or ten have been seen in a single cell. The chromatin network is prominent in these nuclei and one or more large nuclei are always present. The nucleoli always take a contrasting stain to the nucleus. No definite mitotic forms were ever seen. Direct division was frequently observed. The protoplasm is usually homogeneous and stains well. These giant cells, so far as our observation reaches, are peculiar to this growth and are of great assistance in diagnosis.

The work of Reed on the histologic findings in Hodgkin's disease, including the characteristic giant cells, was soon corroborated by Longcope, Simmons,[28] Gibbons,[29] MacCallum, etc. Later Symmers[30] wrote: "In late years Hodgkin's disease appears to have been recognized as a definite histologic entity, characterized by changes which resemble those of the infective granulomas." He suggested as a name for the disease "Hodgkin's granulomatous lymphoma."

Warthin[31] considers that the pathologic conception above described is not typical of all cases of Hodgkin's disease. He has found these changes in only one third of the cases in which the clinical diagnosis of Hodgkin's disease was made. He states that the various forms of generalized and regional lymphocytoma are regarded by some as Hodgkin's disease or pseudoleukemia. Other writers (Reed, Longcope, MacCallum) he says regard as the essential histologic changes a very different process. This is characterized by changes resembling a chronic inflammatory process, consisting of proliferation of endothelial and reticular cells, the presence of many eosinophils and a progressive fibrosis. He agrees that such a pathologic condition exists. He thinks "at the present moment it would appear wisest to limit the pathologic diagnosis of Hodgkin's disease to the chronic inflammatory type of Reed, Longcope, and others, until its etiologic nature is discovered." It is convenient to speak of it, he says, as the endothelioid type of Hodgkin's disease. If this perhaps limited, but defi-

28. Simmons, C. C.: Hodgkin's Disease. A Pathological Analysis of Nine Cases, J. M. Res. 1903, 4 New Series, p. 378.

29. Gibbons, H. W.: The Relation of Hodgkin's Disease to Lymphosarcoma, Am. J. M. Sc. **132**:692, 1906.

30. Symmers, Douglas: Certain Unusual Lesions of the Lymphatic Apparatus, Arch. Int. Med. **4**:218 (Sept.) 1909.

31. Warthin, A. S.: Osler's Modern Medicine, Philadelphia, Lea & Febiger, **4**:729, 1908.

nite conception, is accepted as typical of Hodgkin's disease, there seems no doubt that my case is pathologically one of this class. That it was probably a case of Hodgkin's disease, as shown by the clinical findings, has already been stated.

DISCUSSION OF THE AUTHOR'S CASE

In discussing the cutaneous lesions presented in my case, it is necessary to consider the possibility of lymphatic leukemia and mycosis

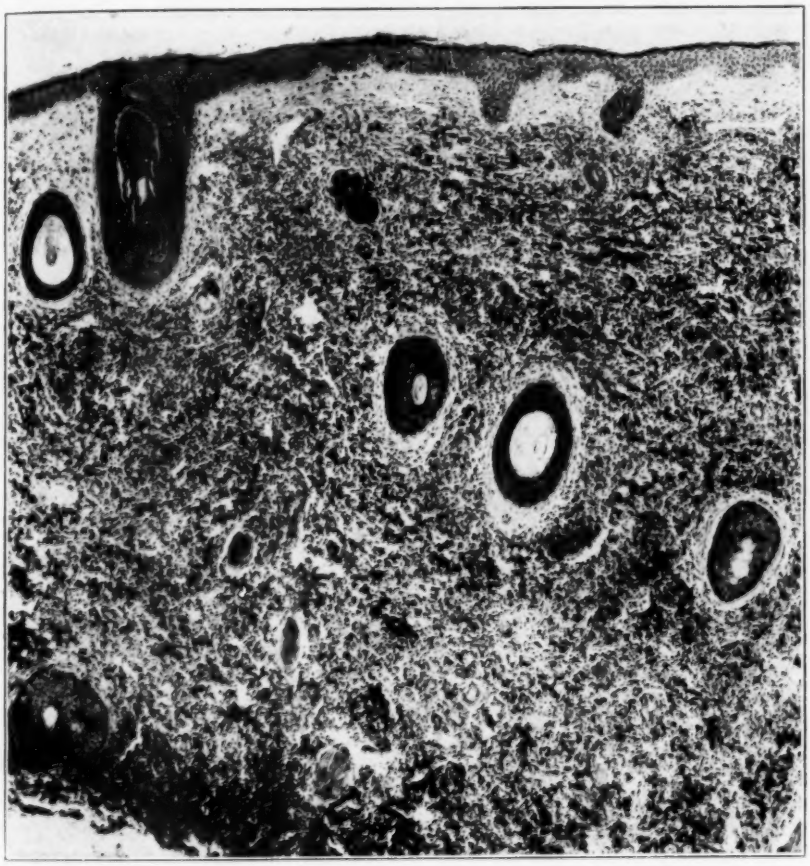

Fig. 3.—Low power. The infiltration extends from the subpapillary vascular plexus to the utmost depths of the tissue and consists of large masses of lymphocytes situated mostly about the vessels. There is a dense background of general infiltration of the same character; the vessels and adnexa are virtually unchanged.

fungoides. A lymphatic leukemia can be almost surely ruled out by the blood picture, as there was no actual or relative increase in the number of lymphocytes. It can surely be ruled out from the histologic findings of a lymphogranuloma. In regard to mycosis fungoides the

problem is more difficult. However, the mode of onset (appearance of tumors without preceding eczematoid or other lesions), the involvement of the lymphatic glands and spleen and the virtual absence of itching, all are against the clinical diagnosis of mycosis fungoides. The presence of the characteristic giant cells in the skin, together with the histologic findings in the lymphatic glands, are strong evidence of a true case of Hodgkin's disease of the skin in the pathologic sense already described.

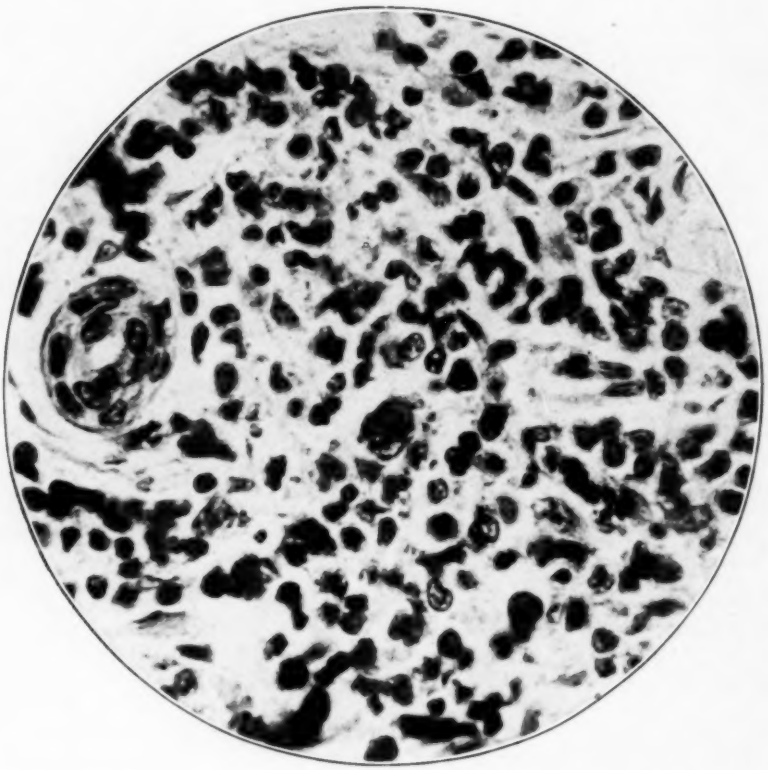

Fig. 4.—High power. In the center of the field is a Dorothy Reed cell. The lymphocytes, particularly in relation to the vessel, are clearly shown.

The patient was presented on February 24 before the New York Dermatological Society (before the result of the biopsy was known) and on March 22 before the dermatological section of the New York Academy of Medicine. At the latter meeting, after describing the histologic findings recorded in this report, Dr. Walter J. Highman said in conclusion that "these findings convince me that the case is one of Hodgkin's disease."

Dr. J. F. Fraser, in discussing the case, said in part that lesions presenting the typical histologic picture of Hodgkin's disease were of very rare occurrence in the skin. He had observed only one case in which the typical Hodgkin's lesion was present in the true skin (Trimble's case quoted above). He believed that many of the cases that had been reported as nodules in the skin were not lesions of the true skin at all but nodes of the subcutis. One of his cases had illustrated this point very well. He said that since Dr. Highman had explained the findings of the characteristic picture in the skin lesions, he was willing to accept a diagnosis of Hodgkin's disease; the so-called Dorothy Reed cell, so far as he was aware, was not found in any other condition. He added that the case "should be recorded in the literature as one showing the typical Hodgkin's disease lesions in the skin."

RELATIONSHIP OF HODGKIN'S DISEASE TO MYCOSIS FUNGOIDES

It may be of interest to touch on the difficult and much discussed subject of the relationship of mycosis fungoides to Hodgkin's disease. Some writers have considered mycosis fungoides a cutaneous form of Hodgkin's disease, an opinion expressed by Ziegler in his monograph. Strobel and Hazen think that mycosis fungoides belongs to the group of lymphomas, including Hodgkin's disease. They state that the "type of Hodgkin's disease, as described by Reed, Longcope and others is essentially different from mycosis fungoides, especially if one regards the epithelioid and giant cells as being really essential characteristics of true Hodgkin's disease." They think, however, that "the essential pathologic picture is the lymphoid proliferation and that the other cell types constitute merely an unimportant variation."

It would appear that mycosis fungoides and Hodgkin's disease are separate clinical, if not pathologic, entities. In the excellent comparative tables of Strobel and Hazen the similarities of the two affections in many respects are rather striking. Mycosis fungoides, however, appears primarily as a disease of the skin, whereas Hodgkin's disease primarily affects the lymphatic glands. The tumors of mycosis, except in rare cases of so-called mycosis fungoides d'emblée (Vidal and Brocq[32]), are preceded by eczematoid and sharply defined erythematous (frequently circinate) lesions. These prefungoid eruptions are not merely incidental, as they show the histologic picture of the disease; they are in fact an early stage of the disease of which the tumors are a later development. The cutaneous manifestations of Hodgkin's disease other than the tumor-like infiltration are the incidental, nonspecific eruptions, most often of a prurigo-like or

32. Vidal, E., and Brocq, L.: Etude sur le mycosis fongoide, La France méd. **2**:946, 1885.

urticarial type. In mycosis fungoides there is always a tendency to necrosis and ulceration, which is not seen in Hodgkin's disease. Another important distinction is the involvement of the spleen, liver and other internal organs (mediastinum as shown by the roentgen ray) which, except in rare instances, has not been noted in mycosis fungoides. Pruritus of great severity is a classic symptom of the prefungoid eruption but this may also accompany the cutaneous lesions of Hodgkin's disease, and indeed occurs in this affection without any visible lesions of the skin.

The opinion expressed by Ziegler that mycosis fungoides represents a cutaneous form of Hodgkin's disease was arrived at from certain resemblances in the histologic picture. Actuated by Ziegler's statement, Arndt reexamined in a critical manner the histologic material from nine cases of mycosis in different periods of development. In all of his cases, some of them studied for several years, a clinical diagnosis of mycosis fungoides had been made. In the "eczematoid" and "flat infiltration" stages he found giant cells corresponding to those of the Sternberg type, except that they were much fewer in number than in Hodgkin's disease. In the nodules and tumors of mycosis, on the other hand, they were entirely absent or only occasionally found after most painstaking search. He also stated that eosinophils are at times present in the early stages of both diseases, but only exceptionally in the tumor stage of mycosis. As they were at times so numerous in the lymph nodes and inner organs, Pick suggested as a new name for Hodgkin's disease "granuloma gigantocellulare eosinophilicum." This condition, it may be added, was not present in my case. Whether the peculiar giant cells of Sternberg (corresponding to the cells described by Reed) are absolutely specific for Hodgkin's disease, Arndt said was not settled, and mentioned Schridde as authority for saying that morphologically identical cells were occasionally present in other granulation tissue. Arndt thought that the characteristic picture of Hodgkin's disease was shown by a profusion of giant cells, polymorphism of the cellular infiltrate and the eosinophilia. In the majority of cases that had been histologically proved as Hodgkin's disease, Arndt continued, the clinical picture of classic mycosis had not been present. On the other hand, such cases had always shown glandular changes, frequently changes in the liver and spleen, fever cachexia, etc., which, entirely apart from the skin lesions, made the diagnosis of Hodgkin's disease probable.

The difficulties that are at times encountered in differentiating both clinically and pathologically between mycosis fungoides and Hodgkin's

disease are well illustrated in a recent article by Dr. J. F. Fraser [33] on the pathology of mycosis fungoides. In one of his seven cases a definite picture of early mycosis was shown by the mode of onset and development, though the case finally showed "clinical and pathologic features indicative of Hodgkin's disease." In analyzing the case, he concluded that the "facts exclude the interpretation of the case as one of Hodgkin's disease with premycosic skin manifestations." He was left with the following three alternatives: (1) that the two diseases existed independently in his case; (2) that they are different manifestations of the same disease; (3) or that they are different diseases caused by agents that can, under certain conditions, stimulate the tissues to very similar reactions. Though unable to decide on one of these hypotheses, he appeared to incline somewhat to the last interpretation.

From the preceding it seems clear that the histologic differentiation between mycosis fungoides and Hodgkin's disease may be very difficult. Whether mycosis should be considered as a cutaneous manifestation of Hodgkin's disease cannot be settled positively until the cause of these diseases has been discovered. That Hodgkin's disease has a "very precise histology" but a "wholly unknown etiology" is the opinion of Janeway.[34] In spite of Bunting and Yates' work, the etiology he says "cannot be considered solved for Hodgkin's disease."

RELATIONSHIP OF HODGKIN'S DISEASE TO TUBERCULOSIS

Finally, regarding the relationship of Hodgkin's disease to tuberculosis: In my case there were no findings that suggested that the disease process was in any way related to tuberculosis. The publication of Sternberg's paper in 1898 was the source of much discussion concerning this relationship, though Fischer [35] had previously concluded on clinical grounds that the Sternberg disease had no relationship to tuberculosis. Space will not permit further mention of this question, which has been thoroughly discussed by Ziegler, Myer [36] and others. In my own case there was no family history of tuberculosis. There was no history of cough, bloody expectoration, night

33. Fraser, J. F.: The Pathology of Mycosis Fungoides, J. Cutan. Dis. **35**:793, 1917.

34. Janeway, T. C.: Hodgkin's Disease with Extensive Skin Eruption, Med. Clin. North America **1**:1, 1917.

35. Fischer, F.: Ueber malignes Lymphom, Arch. f. klin. Chir. **55**:467, 1897.

36. Myer, O.: Beitrage zur Klinik, Pathogenese und pathologischen Anatome des malignen Granuloms, Frankfort. Ztschr. f. Pathol. **8**:343, 1911.

sweats, etc., and a physical examination of the chest was negative. Though the first examination of the lungs showed "apices hazy," subsequent roentgenograms of the lungs failed to show, on careful scrutiny, anything abnormal. The von Pirquet reaction was negative and examination of the spinal fluid showed nothing abnormal. The histologic structure of both glands and cutaneous tumors failed to show either the presence of tubercle bacilli or any structure such as Langhans' giant cells, caseation, etc., suggesting tuberculosis. The result of guinea-pig inoculation of tissue from an excised gland could not be given at the time of reading this paper as the intervening period (four weeks) was not sufficiently long. Guinea-pig killed June 1. Necropsy showed no signs of tuberculosis.

SUMMARY OF CASE

The patient whose history forms the basis of this report was an ex-soldier of the regular Army, 30 years of age, who presented a moderate, painless enlargement of various groups of lymphatic glands, enlargement of the spleen and liver, a normal blood picture, except for a mild anemia, dyspnea on exertion and increasing asthenia. At the time of writing, his illness had existed fifteen months. A histologic examination of an excised gland showed a typical picture of a lymphogranuloma, including the presence of uninuclear and multinuclear giant cells of the Dorothy Reed type. The cutaneous lesions consisted of tumor-like infiltrations of portions of the scalp, forehead and midscapular region. Histologic examination of a tumor from the scalp showed a similar structure to that of the gland. No increase of eosinophils was present in either gland or cutaneous tumor. Thorough examination (physical, roentgen-ray and pathologic) failed to show any evidence of tuberculosis.

CONCLUSIONS

1. If the pathologic conception of Hodgkin's disease is limited to what Warthin speaks of as the "endothelial type," meaning the conditions described by Reed, Longcope and others, this case must be regarded as one of Hodgkin's disease.

2. As the cutaneous lesions showed a similar structure to that found in lymphatic glands, it should be classed as one of true Hodgkin's disease of the skin. This condition has been previously reported in only a small number of cases.

3. This case may be added to those that tend to disprove the contention that Hodgkin's disease is related to tuberculosis.

4. Mycosis fungoides can generally be clinically differentiated from Hodgkin's disease, though at times this may be difficult or impossible. The differential diagnosis, from the histologic standpoint, may also be difficult at a given moment. Until the causes of these diseases are definitely ascertained, it cannot be settled with certainty whether mycosis fungoides should be considered as a cutaneous manifestation of Hodgkin's disease.

In addition to the acknowledgment I have made in this report to those who have given me assistance, I wish to express my thanks to Dr. George M. MacKee for making the photomicrographs and to Drs. W. T. Longcope and S. Pollitzer for reading my manuscript and making valuable suggestions.

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LYMPHATIC LEUKEMIA WITH PRIMARY MANIFESTATIONS OF THE SKIN*

JOHN BUTLER, M.D.

MINNEAPOLIS

In lymphatic leukemia occasionally there are found lymphadenotic infiltrations in the skin and subcutaneous tissues that are a part of the general disease. These infiltrations consist of hyperplastic lymphocytic elements and are generally supposed to be marrow lymphocytes transported by the blood stream and deposited in the skin and subcutaneous tissues. These lymphadenotic skin changes occurring in, or preceding, a lymphatic leukemia are of two forms: the circumscribed, or tumor, and the diffuse, or universal. The first is a nodular, or tumor form, or a circumscribed leukemic, or aleukemic, lymphadenosis of the skin. The second is a diffuse or universal leukemic, or aleukemic, lymphadenosis of the skin. Sometimes we find generalized skin affections, as purpura, prurigo, urticaria, pruritus and generalized exfoliative dermatitis, associated with or preceding a leukemic condition. The differentiation of this group of affections from like processes in no way related to a leukemia is impossible by means of clinical and histologic studies only, and every patient showing such chronic lesions, in the absence of an etiologic factor, should have a blood examination at different times to determine the possible existence of a leukemia. In a recent paper by Arndt,[1] he discusses skin changes in leukemic conditions; he suggested a revision of the nomenclature by dropping the terms lymphatic, and myelogenous, leukemia for the reason that the blood in cases so designated may be normal at times. He recommended as a substitute the terms leukemic, aleukemic and subleukemic lymphadenosis, which would allow a correct comparison of the blood changes with the lymphadenotic changes in the various organs involved. Therefore he designates according to the blood picture: First, aleukemic lymphadenosis when the organs are infiltrated and the blood picture is normal; second, subleukemic lymphadenosis, if the number of white cells in the blood is normal or very little increased but the proportion of the lymphocytes is increased; and third, leukemic lymphadenosis when there is an absolute permanent progressive increase of lymphocytes in the blood and the total number of leukocytes is augmented.

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* Read at the Forty-Third Annual Meeting of the American Dermatological Association, Asheville, N. C., April, 1920.

1. Arndt, G.: Dermat. Ztschr. **18**:53, 1911; Diseases and New Growths of Lymphatic Origin, J. A. M. A. **63**:1268 (Oct. 10) 1914.

Strobel, E. R., and Hazen, H. H.: J. Cutan. Dis. **29**:147, 1911.

These lymphadenotic skin changes are in no way synchronous with or dependent on the blood changes and they may be the first and only recognizable symptom of leukemia or preleukemia. Therefore, in considering skin affections that may be of leukemic nature, it is important to bear in mind that the blood picture may be absolutely indifferent to the aspect or cytology of the cutaneous lesions. The evolution of the skin lesions generally follows the evolution of the leukemia; however, they may occur at any time, sometimes in the beginning, sometimes in the course of the disease or in the final stage. They may occur before or after lymphatic, glandular or splenic involvement. They precede the blood changes in many cases, which may lead us to consider the cutaneous foci the starting point of the disease. If there is visceral hypertrophy, it may escape notice and the cutaneous affection not only may be the first symptom to appear, but may seem independent of visceral change, and the visceral involvement may only be evident at necropsy. Sometimes the cutaneous manifestations in leukemia are neglected by both patient and physician and are considered as trivial incidents, or they may dominate and mask the general malady. This surely emphasizes the importance of a careful examination in diseases characterized by skin affections which may be associated with alterations in the hematopoietic system.

A histologic examination of the lesions in the circumscribed form reveals alterations that consist of a dense and compact infiltrate which has the morphologic qualities of small or large lymphocytes; accumulations of these lymphocytes occur around the vessels, principally where the blood supply is abundant, as around the follicles and glands. These lymphatic foci coalesce and form infiltrative masses. There is a very sparse production of connective tissue in the vicinity of such lymphadenotic formations. The process spreads about the vessels to the reticular dermis and the subcutaneous tissues; there is a zone of normal texture between the reticular layer and the epidermis.

The histology of the diffuse or universal lymphadenosis of the skin discloses similar alterations, but it differs in this, that there are diffusions in the whole cutaneous integument; the original connective tissue is pushed aside and replaced by lymphocytes and there is no proliferation of the connective tissue. We find a pronounced cellular polymorphia, numerous small lymphatic lymphoblasts and more rarely large and atypic forms; the papillary and subpapillary layers show dilated blood vessels and pronounced edema with little or no infiltrations. Numerous mitoses may be observed in these cases in contradistinction to the circumscribed type, where they are rarely observed.

Up to the present time there have been recorded in all of the available literature less than one hundred cases of lymphatic leukemia with associated lymphadenotic skin lesions. Of those recorded, about

half were observed in cases of acute lymphatic leukemia and about the same number in the chronic type. In most of these cases, the blood changes preceded the skin changes. About 90 per cent. of all the contributions on leukemic skin affections are reported in the German, French and Italian literature.

I report herewith a case of lymphatic leukemia following lymphadenotic skin changes of the circumscribed or tumor type. There were many interesting features in connection with this case that may be summarized before describing it in detail. The disease began apparently with a throat infection. The first evidence of the disease was the development of the skin tumors. The blood picture was normal at the beginning of the disease. There were no blood changes until all of the skin tumors were formed. Glandular and visceral involvement was not apparent in this case at any time. The skin tumors were made up of collections of large lymphocytes. When all the tumors were formed the blood showed a leukemia for the first time. The lymphocytic deposits showed numerous mitoses. The benzol treatment caused a partial regression and paling of the tumors.

REPORT OF CASE

History.—Miss R., aged 35 years, was first seen by Dr. W. J. Byrnes, April 14, 1916. Her father died of pneumonia at the age of 56. She was survived by her mother, three sisters and two brothers, all of whom were in the best of health. The patient had always been in excellent health except for an attack of diphtheria at 12 years; since that time she had not known a sick day until April 14, when she called on Dr. Byrnes. She complained at that time of a slight sore throat and some pain in the back of the neck and in the right shoulder. She had a temperature of 101 F., and the condition was assumed to be rheumatic. The pain in the neck and shoulder diminished in a few days and the temperature became normal. On April 29, she had another attack of sore throat and a temperature ranging between 102 and 104 F., which lasted for three days. While Dr. Byrnes was attending her for this attack she called his attention to a painless subcutaneous tumor, the size of a dime, on the flexor surface of the right forearm. This tumor involved the overlying skin, was slightly raised and reddish brown. Dr. Byrnes made a careful examination and could discern no other tumors, cutaneous or subcutaneous. The sudden rise of temperature of three days' duration dropped to normal, and the patient felt comfortable. A few days later, there developed two similar tumors under the right shoulder blade and three over the sternum. At this time, she showed a slight loss of weight, she became slightly pale and the temperature was normal in the morning but ranged between 99 and 100 in the afternoon. The last week in May, approximately one month after first calling on her physician, numerous tumors began to develop on the face and extremities. These tumors were more readily palpated than seen and the overlying skin was of normal color. A blood examination was made at this time, but revealed no abnormalities.

Examination.—From this time on the tumors began to take on a livid red color, and the patient began to show marked anemia and weakness. The tumors multiplied rapidly, and the patient was confined to her bed. I saw her in

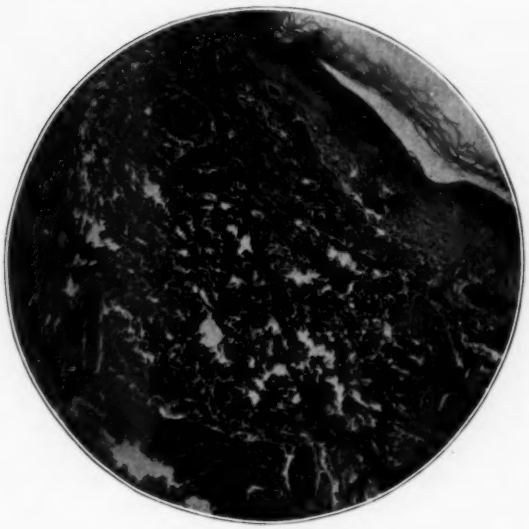

Fig. 1.—Section of nodule under low magnification, showing the small cords and nests of lymphocytes in the superficial part, separated by a fibrous connective tissue. The cell nests in the deeper portion are larger.

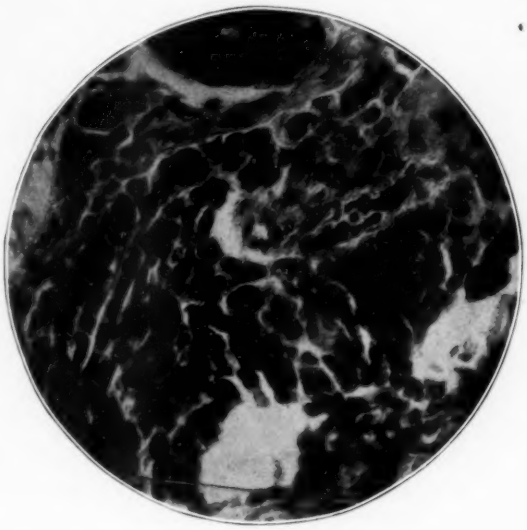

Fig. 2.—Large cell nest from deeper part of nodule under high magnification. The cells are of lymphatic type and are closely packed.

consultation with Dr. Byrnes on July 19, 1916. She was a slender woman weighing about 115 pounds; her normal weight was 130 pounds. The first impression on looking at her was the striking resemblance of her face to the characteristic leonine facies of the leper; the extreme paleness was the only distinguishing feature that would make one hesitate in making a snap diagnosis of nodular leprosy. Closer examination revealed the presence of from twenty-five to thirty subcutaneous tumors, varying in size from that of a pea to that of a hazelnut, which were of a waxy, gray-yellow translucent appearance and doughy in consistency. The tumors protruded slightly above the skin surface. Many of them involved the skin, others were subcutaneous, not visible, but easily palpable. They were most numerous on the eyebrows, eyelids and forehead, where they raised the skin in folds. The cheeks were singularly free; the chin and neck showed more circumscribed formations. The lymphatic ring around the mouth was evenly infiltrated, suggesting a ring of coalesced subcutaneous tumors. The body presented about 500 such tumors. These were much larger than the lesions on the face, measuring from 2 to 5 cm. in diameter. They were rather flat-topped, round or oval

Results of Blood Examination

	Disp. Clinic July 15	Dr. Head July 28	Dr. White Sept. 1	Dr. Head Sept. 5	Dr. Rizer Sept. 12
Hemoglobin	65%	55%		24%	25%
Erythrocytes	3,200,000	2,750 000	1,496,000	1,900,000	1,500,000
Leukocytes	5,000	3,000	40,730	52,000	52,800
Polymorphonuclears	63%	67%	2.6%	3.5%	3.5%
Large lymphocytes	2%	3.5%	77%	91.5%	92%
Small lymphocytes	29%	26%	12%	4.5%	4.5%
Transitionals	1	0.5		0 5	
Eosinophils	4.0	2%		0.0	
Myelocytes		0.0			0.0
Normoblasts	.....	.....	.....	1 in 200 cells	
Megaloblasts	.....	2 in 200 cells	.....	1 in 200 cells	
Poikilocytosis	.....	present	.....	0.0	moderate
Anisocytosis	.....	present	.....	present	moderate
Extruded nuclei	.....	.....	8.3	.....	No nucleated reds

raised patches of firmer consistency than the tumors on the face. The skin between the tumors appeared normal. All of the tumors on the body were a cyanotic or livid red. On the extremities, the tumors were somewhat smaller and oval in contour, and of even firmer consistency than the body lesions. Their color varied from a rose red to a cyanotic reddish-brown or blue. The lesions around the feet were larger and their borders were of a grayish blue with a hemorrhagic border, not unlike the patchy lesions observed in Kaposi's hemorrhagic sarcoma. A notable peculiarity of the tumors on the body and extremity was that the benzol treatment would make the color fade from them temporarily, so that they resembled the face lesions in color at times.

Dr. George Douglas Head saw this patient with me on July 20, when he made a complete physical examination. He kindly gave me his findings, which are as follows:

The patient, an intelligent girl, was tall and thin. The pupils reacted to light, the knee jerks were present.[2] There was no swelling to be made out along the long bones. A careful examination was made for enlarged lymph

2. Dr. Head made an extensive report on the skin condition which agreed with my description of the skin tumors.

glands or metastatic growths in the bones, but none could be found. The spleen was just palpable at the costal margin; the liver was not enlarged. No distinct masses could be made out in the abdomen. The patient's tongue was fairly clean. There was no swelling of the lower limbs. The patient was distinctly emaciated. The heart was negative; nothing was made out in the lungs; there was no cough. There had been no bleeding of the gums, no nosebleed or bleeding elsewhere since the illness came on. The mucous membranes were free; there was nothing in the throat.

Fig. 3.—Lymphadenotic tumors on forearm: the large tumor is the primary lesion.

Fig. 4.—Lymphadenotic tumors on lower extremities, showing the hemorrhagic borders of tumors on the foot.

Dr. Head, Dr. S. Marx White and Dr. Robert J. Rizer kindly made blood examinations in this case at different times which were very interesting. The Wassermann reaction was negative. Their findings are recorded in the accompanying table.

A small vertical section was cut out from a nodule, fixed immediately in Zenker's fluid and examined by Prof. E. T. Bell, in the pathologic department of the university. The tissue was embedded in paraffin and the sections were stained with hematoxylin and eosin.

Under low magnification (Fig. 1) the deeper part of the dermis and a thick layer of the underlying subcutaneous areolar tissue were seen to be densely infiltrated with cells of a lymphatic type. In the deeper parts of the nodule, the cells often were arranged in large nests; in the parts nearer the epidermis, they were usually arranged in small nests or cords. A dense fibrous connective tissue separated the groups of cells. The cellular infiltration did not involve the superficial part of the dermis.

When examined under high magnification (Fig. 2), the cell nests were found to be composed of closely packed cells of lymphatic type. The nuclei were spherical or ellipsoidal and contained considerable chromatin. There was an abundant cytoplasm. Where the cells were closely packed, no cell boundaries were visible, but where they were less crowded all cells were distinct. In some areas, mitotic figures were frequently observed. The cells were of the type commonly found in organs, such as the liver and kidneys, in cases of lymphatic leukemia. The presence of mitotic figures indicated that cell multiplication had taken place in these foci.

Clinical Course.—The patient became ill first on April 14, and died, September 17. She was confined to her bed permanently after June 18. Her pulse ranged between 105 and 120 throughout her illness. She had no hemorrhages during her illness. Her chief complaint was a constant diarrhea, which persisted after the withdrawal of arsenic. Her appetite was very poor, and milk was the most suitable and sustaining food she could take. The tumors caused her no inconvenience; none of them ulcerated and there was no itching. The urine was normal except for a great increase in uric acid in the later stages. Two weeks before death, she became deaf in the right ear. She became comatose on the evening of September 16, and died the following morning. It was extremely unfortunate that a necropsy was not permitted.

COMMENT

It is hardly within the scope of this paper to speculate on the cause of lymphatic leukemia. The history and course of this case surely suggest an acute infection. It is generally understood that the bone marrow is the starting point of the disease, but in a case like this we must consider whether the lymphocytic collections which make up the tumors were manufactured in the bone marrow and deposited in the skin by the blood, or whether the skin could of itself manufacture lymphocytes at the expense of its own lymphatic centers. Admitting in this case that the bone marrow was primarily involved, would it argue against an independent lymphatic hyperplasia in the skin? If the skin infiltrations were bone marrow lymphocytes, why should the blood picture be normal up to the time, and even after the time, that all of the skin tumors had formed?

Another point worthy of careful consideration in this case was the apparent lack of involvement of other tissues and organs than the skin, during both the aleukemic and leukemic stage of the disease.

The occurrence of numerous mitoses in the lymphocyte nests argue for the local proliferation of the tumors. If we concede in this case

that the primary changes took place in the bone marrow, it would not alter the fact that there is an independent lymphatic hyperplasia in the skin.

These facts would suggest that the skin may of itself undergo lymphoid transformation which would be contributory to the development of a lymphatic leukemia.

DISCUSSION ON PAPERS OF DRS. FOX AND BUTLER

DR. WILE expressed his appreciation of Dr. Butler's paper because he was more particularly interested in that. He had under his care at present a most extraordinary case of lymphatic leukemia which, except for one other, was a unique case. Dr. Engman had seen the patient and could substantiate the diagnosis. The patient's disorder started with a simple exfoliative dermatitis six years before admission to the hospital, and he had been treated for eczema. This was followed by a marked pruritus. The skin began to exfoliate in 1916 at which time he had been given a dose of arsphenamin, which made the exfoliation worse. The man entered the hospital in 1919, and a diagnosis of desquamative dermatitis was made, there being no other sign of trouble. Shortly after his entrance, he developed a lymphatic enlargement, which was so pronounced that it could not be associated with the skin primarily. The blood picture up to the time of the lymph gland involvement was negative. It then revealed a very marked lymphocytosis, with a great preponderance of lymphocytic cells. The patient now presented the picture of lymphocytic leukemia. Dr. Wile was inclined to believe that the exfoliative condition may have acted as an insult which produced a condition simulating lymphocytic leukemia in the blood. Later the true picture of lymphatic leukemia appeared, with enormous enlargement of the liver and spleen, and now large nodes had developed on the skin.

There are two types of cases which one encounters: In one, as in Dr. Butler's case, there was the true primary leukemia of the skin, and in the other, to which Dr. Wile's case belonged and perhaps that of Nikolai, they were dealing with some insult to the skin with so-called secondary leukemia. His patient had received arsenic with absolutely no benefit to the condition, and he was also febrile.

Dr. Wile showed photographs of his patient.

Dr. Wile stated that the histologic sections taken from four different parts were studied and showed a typical picture of lymphatic leukemia, as did also an excised gland.

DR. WENDE stated that he believed that as shown by the photographs, one of his patients, aged 64, had lesions corresponding to the type described by Dr. Butler. The lesions were distributed over the entire body and although the patient was not continuously under his care the lesions seemed to conform to those in Dr. Butler's case.

Dr. Wende referred to his publication in the *American Journal of the Medical Sciences* in 1901, of the report of a case of lymphatic leukemia developing from a case of Hodgkin's disease and culminating in streptococcus infection. In this case the lesions corresponded to those in the case of leukemia just reported by Dr Butler and also to those in the case of Hodgkin's disease just reported by Dr. Fox. Dr. Wende stated that he then (1901) directed attention to the indefinite and unsatisfactory classification of lymphosarcoma and pseudoleukemia; and that there was a possibility of an

aleukemic stage preceding a true leukemia. The presentation today of the two dissimilar cases with such similar tumor lesions had again brought the contention of that time to the fore. Nevertheless, from the pathologic findings in his case and in that of Dr. Fox he did not think that they were in any way allied. His own case, when the patient was first seen, corresponded clinically to Hodgkin's disease, but the tumors were due mostly to lymphocytes that he then stated, and that he still believed, escaped into the skin through rents in the blood vessels, which opinion was subsequently concurred in by Walsh and others. The patient had typical nodular infiltrates, and when the condition developed into acute leukemia it presented other manifestations such as the generalized purpura, the itching and many of the other manifestations referred to by Dr. Fox.

Dr. Wende expressed his appreciation of the privilege of hearing the papers of Drs. Fox and Butler because taken in connection with the case reported in 1901, the clinical pictures presented by all three were so very similar that they led to the false impression that they were but different manifestations of the same etiologic factors; however, the morphology in each of the cases positively determined that they were of different entities.

Dr. Fordyce said the cases so carefully reported by the authors will undoubtedly help to give us a clearer idea of the skin conditions connected with the blood making organs. It was not so difficult to diagnose the skin changes when they occurred with the blood picture of leukemia. In the undeveloped leukemic state it was very difficult to correlate the skin condition with that disease unless repeated examinations were made, as had been made by Dr. Butler. He had at present under his observation a number of patients with generalized thickening of the skin associated with enlargement of the inguinal and axillary lymph nodes. In two of these cases a moderate leukocytosis with a relatively high lymphocytosis was present while in the third no blood change was found. How are we to classify such cases? Is the leukocytosis and associated lymph node enlargement due solely to the generalized skin inflammation or are both conditions due to an underlying disturbance of the hematopoietic system? He believed only prolonged observation with repeated blood examinations could elucidate this problem. It seemed to him important to restudy the entire group of erythrodermias and their relationship to the blood forming organs.

Dr. Grindon was interested in Dr. Butler's case because it vividly brought to mind a case of lymphatic leukemia which he observed many years ago, when he did not have the training necessary either to investigate the case as it should have been investigated, or to appreciate what he saw. Later the true nature of the case became very evident. The patient was 62 years of age and had always enjoyed perfect health. The disease began with pruritus chiefly about the scalp and face, so that the patient in seeking to relieve it acquired the habit of pulling out the hair of his beard and scalp, producing bald areas here and there. The pruritus later extended over the entire surface. The earliest portion to be involved was the face, and the lesions here remained throughout more marked than on other parts, although they were generally distributed. There was marked leontiasis; the skin about the forehead and face was thrown into thickened folds. Tumors of various sizes developed, some of them discernible only on palpation, others that could be seen and were generally discolored. Some were pink or red while others changed to a yellow or brownish hue, or even a light hemorrhagic tone. In places on the face were masses as big as a silver dollar, soft to the touch and depressed

in the center. On the body were also numerous lesions, some that could be felt only, others that could be seen but that were without discoloration. Others were of a variety of colors, but there was not the play of color on the body that was present on the face. Some of the body lesions would become as large as a hen's egg or larger. There was enlargement of the lymph nodes, more particularly the axillary and inguinal, but also at other points. One characteristic of these lymph node enlargements was their great hardness. The pruritus was most distressing—as bad as in mycosis fungoides. A striking picture of the case was the change which it underwent, both as to individual lesions and as a whole. The lesions would grow to a good size and then flatten out, leaving little discoloration. Later, new lesions would come up at the same or other sites. The case went through a great variety of changes. At one time the lesions would suddenly disappear, to reappear after a few days. Again marked anemia developed for a time. The patient lived for thirteen years and died of an intercurrent disease. For some time before death, he was much improved, under practically no treatment.

Dr. Highman said that these two papers had brought to the fore once more one of the most interesting phases of dermatology, namely, the need for remaining good internists as well as dermatologists. In leukemia cutis one might know what he was talking about in the leukemic stage, but in the aleukemic, or subleukemic phases of the disease one was immediately confronted by the relationship with mycosis fungoides and Hodgkin's disease. Hodgkin's disease was very closely allied to mycosis, particularly mycosis d'emblée as Dr. Fox pointed out. There were six very important works on this subject, three by Europeans, Paltauf, Audry and Arndt, and three by Americans, Hazen, Cole and Frazer. It seemed to him that for the time being one had to be very conservative about mycosis in relation to leukemia and Hodgkin's disease. Dr. Fox's case was unique in that while it was not the first case of cutaneous Hodgkin's disease on record, he thought it was the only case in which Dorothy Reed cells had been found in the skin. In the gland section he could not find nearly so much evidence of Hodgkin's as in the skin, although the gland studied in Schenectady showed Hodgkin's disease. He examined a series of slides of Hodgkin's glands, and it seemed that the longer the duration of the disease, the less characteristic were the gland lesions, although one could always find some Dorothy Reed cells.

Dr. Highman thought it would be necessary to consider leukemia as a disease of an entirely unknown origin, inasmuch as some forms develop that act just like an acute infectious disease with hemorrhages in the skin and fever.

Dr. Hazen said that there were five conditions which were sometimes confused with Hodgkin's disease: in the first place, tuberculosis, which could be excluded; in the second place, lymphosarcomatosis, which may or may not be like Hodgkin's; in the third place, cases that may be preleukemia or aleukemia; in the fourth place, what may be simple lymphomas, as described by Warthin, and the last, those with Dorothy Reed bodies, true Hodgkin's disease. The cases with preleukemic or aleukemic conditions have been recorded more often by dermatologists than by hematologists and internists combined. The question was whether there was some traction which took those cells out of the blood and caused them to be deposited in the skin. In regard to the blood findings that were supposed to be typical, we should be very skeptical. He had seen one case in which three blood smears were taken on the same day and sent to different pathologists. Bunting reported more than any other pathologist could find. Tumors were taken out and found

to be typically tuberculous. One thing about mycosis fungoides to which Dr. Highman originally called his attention was rather interesting. That was that at first there is apparently a generalized stage similar to leprosy and syphilis, and then fewer but ulcerative lesions. In the leukemias there were two classes: the first, the acute cases with the marks of an infection in which the leukocytes do not exceed from ten to fifteen thousand, and if there is any increase in lymphocytes it is principally of the large varieties; the second, the chronic cases with the increased small lymphocyte counts. Between these two are various stages in all of which it is impossible to tell whether one is dealing with the acute or chronic stage. Dr. Hazen called attention to the work of Türck who had emphasized all this and pointed out that the disease might change from the aleukemic to the leukemic stage and might occur within a short interval. The whole subject was fraught with difficulty at the present time.

Dr. Hazen was very glad to have heard both of these reports, and said they were cases that had been admirably worked up.

Dr. Hartzell believed we should distinguish between true leukemic conditions of the skin and toxic eruptions occurring in leukemic subjects. In one case under his observation recently in which there was a leukocytosis of 130,000 with 70 per cent., or even higher, of lymphocytes, there had been a continuous eruption which was most abundant over the buttocks, the thighs and in the popliteal spaces, which in the first twenty-four hours looked much like the wheals of urticaria. Later, some of the lesions became hemorrhagic; at times there were bullae on the forearms. After the lesions had existed for a few days, they resembled the large, flat papules occasionally seen in erythema multiforme. There was no itching except in cold weather when there was moderately severe pruritus. Sections made of these lesions had shown very little histologic change. There was a very scanty perivascular exudate and some edema. There was no infiltration of the skin with lymphocytes; here one had to do with a toxic eruption. The patient was given benzol, with no benefit, but radiotherapy produced an enormous improvement in the blood count but none in the patient. When the patient was seen within a month or two, he had only 7,000 white cells, but the relative proportions of the cells in the differential count remained about the same.

Professor Lindenberg said he considered leprosy very similar in appearance to leukemia. He had a case in which there were spots all over the body which were not anesthetic. In the histologic examination they found giant cells, which was very rare in leprosy, so they believed the case was one of mycosis fungoides. A year later he saw the patient again and found that the spots had enlarged and become anesthetic in the center. He then thought it was leprosy and found the organism in great quantities in the lesions. This was undoubtedly a case of leprosy which seemed very like mycosis fungoides in the beginning.

Dr. Cole was much interested in both of these papers for each case seemed unusual. He believed Dr. Fox's case was one of true Hodgkin's disease or lymphogranulomatosis involving the skin and considered it a pity that internists were not more interested in the cutaneous manifestations of these diseases. Last year he went into the medical ward of a Cleveland hospital and found a case of lymphatic leukemia with quite marked skin infiltration. Recently he found two cases of Hodgkin's disease side by side in a hospital, one with a very nice prurigo-like exanthem. These cases were

closely related; he had seen transitions forward and back. If the Association made a careful survey and reported yearly on these cases, light might possibly be thrown on the matter and a definite advance might be made as to the etiology of the conditions.

DR. STOKES said that two recent textbooks contained an illustration of leukemia cutis taken from a patient who later came under his observation. This patient had died of Hodgkin's disease. If anyone used the picture again he believed it would be worth while to state that while the picture did resemble leukemia cutis the patient died of true Hodgkin's disease.

Dr. Stokes said it was a pity that some mention of therapy should not be made. Dr. Cole had brought out a valuable point that internists should be stimulated to recognize the early cutaneous symptoms particularly of Hodgkin's disease. He thought it a crime for anyone to see a dermatitis with intense pruritus and not investigate the glands and find out whether the patient had Hodgkin's disease or lymphosarcoma. Enormous doses of radium had radically modified the prognosis of Hodgkin's disease, and for a clinician to go up and down a ward, time and time again, overlooking the possible meaning of generalized pruritus and early exfoliative erythrodermias was to condemn to death patients who might have had considerable prolongation of life, if not cure, with early diagnosis. In the roentgen-ray examination of the thorax in patients who were suspected of having Hodgkin's disease it was essential to realize that mediastinal masses in Hodgkin's disease were not always visible. In his patient the mediastinum was absolutely solid, but the roentgenogram revealed nothing but lateral displacement of the mediastinal tissue, due to a collapse of the lung, secondary to hydrothorax from lymphatic stasis.

DR. POLLITZER said that he had seen Dr. Fox's patient and the slides and that he believed there was no doubt that it was a true case of Hodgkin's disease with lesions in the skin. Two points were of particular interest: first, in his experience, the value of treatment with roentgen rays. He had had for the last two years a patient with leukemia whose sole lesions were of the urticarial, vesicular and occasionally bullous and hemorrhagic-bullous type. The eruption was definitely controlled to the extent of complete freedom from any lesions for many months at a time by systematic radiotherapy directed to the enlarged lymphatic glands.

The second point of interest was the great frequency with which lesions of the tonsils were mentioned; apparently infections of the tonsils which sometimes preceded for many months the first appearance of any lesions which would suggest a diagnosis of leukemia.

DR. ENGMAN said it was very interesting to follow the relationship between the experimental animal tumors, especially those of the dog, and the so-called sarcoma. The trouble is that they are all morphologists and are splitting hairs on the morphologic appearances of tumors or eruptions, and not studying what is back of them. This group is much confused, and no one can entirely differentiate them. He had had an opportunity to study a comparatively large number of cases of mycosis fungoides and leukemia cutis and a few cases of Hodgkin's disease with eruptions. It appealed to him that leukemia of the skin was a distinct entity and did not change its morphologic appearances like some others which were mistakenly put in this group. Maud Slye's studies of mice cancers, in which some strains would run carcinomas and some leukemia, were interesting from this standpoint. It is very pos-

sible that some stimulus might incite the growth of blood cells in one person and epithelial cells in other persons. At the Skin and Cancer Hospital they had several times encountered carcinoma and sarcoma in the same person. In the group, the stimulus, whatever it is, whether micro-organism or chemical change that causes the growth of these cells, might stimulate one group of cells or another, and the question might hinge on one of localization of cell stimulation. Leukemia, as Warthin and Dock have pointed out, might begin in the skin or in another portion of the body with a secondary blood picture. In postmortem appearances, mycosis fungoides and leukemia differ widely. In one case of leukemia where the first symptom occurred as a small tumor on the forehead, the postmortem changes showed involvement throughout all the viscera. Mycosis fungoides never showed a blood picture anything like that of leukemia; and Hodgkin's disease may also be differentiated in this way. Dr. Engman believed the thing that should be done was to generalize more, and not to split morphologic hairs.

Dr. Howard Fox in closing, said it was a great pleasure to have heard the very interesting and pertinent discussion on these two papers. It was a great personal satisfaction to him to have had the diagnosis, in his case, concurred in by those who had given special study to this particular subject.

He believed that very little progress in differentiating Hodgkin's disease and mycosis fungoides would be made until the causes of these diseases were determined. None of the work along these lines was conclusive, including that of Bunting and Yates, and the etiology of Hodgkin's disease still remained unknown.

In answer to one of the speakers he said that his own case was not unique in showing the presence of so-called Sternberg or Dorothy Reed cells, but that in the few reports of cases quoted in his paper, these cells had been found.

Dr. Butler, in closing, said he was very much pleased with the admirable discussions of these two papers. A point of interest was that in both the tumor and universal forms of leukemia cutis the histologic picture showed similar alterations but that one form never went over into the other. In looking over the literature he found that in cases of the universal form the skin sections showed numerous mitoses, whereas, in the tumor form they were rarely observed, this case being an exception in that mitoses were numerous.

XVI.—SOME STUDIES ON LICHEN PLANUS

BASED ON THE STUDY OF ONE HUNDRED AND SEVENTY-NINE CASES *

FRED M. JACOB, M.D.

ST. LOUIS

The literature on lichen planus is large but, except for a very few phases, the entire condition is still open to discussion. The papers by Little and White read before the American Dermatological Association and the discussion which followed included the opinions of many dermatologists on this condition. All agreed as to its typical histologic picture and its usually typical but sometimes multiform clinical manifestations. This multiformity was well demonstrated by Fordyce and MacKee in a series of photographs and in their accompanying discussion.

The etiology, symptoms, course and treatment of lichen planus has caused much and diverse comment. Starting with the early writers we find controversy as to whether its cause is microbic or neurotic. Most of these believed in the neurotic etiology though the histologic picture led some to infer it was infective. Lassar claimed to have demonstrated a bacillus in the lymph spaces of the corium, but this finding was never corroborated, so that the belief that lichen planus was a neurosis gradually gained ground. Of late, however, many men have expressed doubt concerning this theory. Engman and Mook quoted several cases and advanced some arguments in favor of the microbic theory. They also called attention to the granulomatous character of the lesion. In the discussion mentioned in the foregoing, Hartzell, Pusey, Trimble, Pollitzer, Lieberthal, Mitchell and Gilchrist all expressed the opinion that the condition was an infective one. On the other hand, a number of men are of the opinion that the theory of the nervous or functional origin of the condition has by no means been disproved.

The course of both treated and untreated cases varies considerably. Little cites one case in which the condition had existed fourteen

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* Studies, reports and observations from the Dermatological Departments of the Barnard Free Skin and Cancer Hospital and the School of Medicine, Washington University, St. Louis, Mo., U. S. A., service of Drs. M. F. Engman and W. H. Mook.

years before the patient sought the advice of a physician. Fordyce and MacKee believe that the disease is self-limited and that in most cases it will disappear within a year whether treated or not. The most pessimestic view as to prognosis is found in Tilbury Fox's textbook. He states that in some cases marasmus and death would be the outcome. In treated cases the course varies considerably as also does the treatment in the hands of different men, and variations are likewise found in the records of symptoms, both local and constitutional.

The following series of cases is presented principally as a statistical study and also for the interest there may be in their histories and the results of their treatment. These case reports were taken from the records of the Barnard Free Skin and Cancer Hospital, Washington University Dispensary, and from the private files of Drs. Engman and Mook; the treatment was the routine followed in these places. The great majority of the cases were definite, usually quite typical examples of lichen planus, while in a few atypical cases the final diagnosis was reached after thorough study. As many of these cases were referred for diagnosis only, and others were referred for a single exhibition to the students, the histories of a few are not as complete as one could wish, thus making it impossible to have absolutely accurate figures in the statistical tables, and apologies are offered for any slight discrepancies which may be present.

The total number of cases was 179, of which 121 were seen in the clinic and 58 in private practice. The percentage of incidence approximates 1.25 per cent., which is in accord with the findings in other series. There were 110 females and 69 males, which shows the usual predominance of the condition in women. The majority of the women were housewives and very few of the others were engaged in hard labor. Several farmers, an engineer, a huckster and a few others were engaged in outdoor work, but most of the patients were employed as clerks or in some indoor capacity. All statistics on this disease show that it is far more prone to affect indoor or mental workers rather than those engaged in outdoor or manual occupations.

Only five negroes are presented in this series, which is a small number when one considers the large numbers of negroes who attend these clinics. However, the negro does not seem to be frequently affected, for neither Little nor White refer to a case in a negro, while Gilchrist says that possibly only half a dozen cases were recorded in the Johns Hopkins Dispensary in the last twenty years. The eruption in the negro is typical in every respect except in color, which depends a great deal on the degree of pigmentation of the patient's skin. The very dark skins show a grayish papule which has a typical morphology.

The duration of the eruption before the patient presented himself for treatment varied considerably in the different cases. Generalized cases were seen within a few days or weeks after the outbreak of the eruption, but in some of the localized cases the lesions were present for months or even years before the patient was seen. The cases where lesions first appeared in the mouth always had a history of long duration. In one case a lesion in the mouth was present for two years and then came to treatment only because a general eruption of papules had occurred. Another case gave a history of having had a dime-sized lesion on the outer side of the right knee for four years before other lesions appeared, while a third patient presented a hypertrophic lesion, 12 by 6 cm., on the outer side of the thigh, which had been present for nine years. Many cases had been treated, seemingly cured, and had one or more relapses, but there are in this series no records of cases which healed spontaneously.

AGE INCIDENCE

The youngest patient was a girl of 2 years, who had an eruption on the buttocks which appeared some weeks after her mother had been under treatment for this condition. The youngest hyperthropic case was in a child of 14 years. Both of these patients are somewhat younger than are usually found. The oldest patient was 77 years of age and had a case of the hypertrophic variety. In Table 1 may be found the percentage of cases, both typical and hypertrophic, which occurred in the different decades of life.

TABLE 1.—INCIDENCE OF TYPICAL AND HYPERTROPHIC LICHEN PLANUS AT VARIOUS AGES

Decade of Life	All Types Per Cent.	Hypertrophic Per Cent.
First	2	..
Second	8	4
Third	20.3	10
Fourth	18	25
Fifth	25	20
Sixth	17	30
Seventh	7.3	7
Eighth	2.3	4

These figures show that both typical and hypertrophic cases are most frequent in the fourth, fifth and sixth decades of life. The very marked diminution in hypertrophic cases in the seventh and eighth decades cannot be accounted for, as one would expect old people to be more prone to hypertrophic lesions.

PRURITUS

The pruritus varied from an almost unbearable symptom to practically none. One localized case suffered so from pruritus that he hacked the lesions with a knife to relieve his distress.

DISTRIBUTION AND TYPE

Thirty-eight cases showed a generalized eruption of typical papules on all parts of the body, many of them having lesions on the mouth and on the penis; a very few showed face lesions and none, scalp lesions. The appearance of the papules was typical and requires no description here. Five other generalized cases exhibited, along with the usual flat papules, numerous hypertrophic lesions which differed only in their accuminate character and their lack of a flat shiny top. The remaining cases showed either a single lesion or patch of lesions, or a few scattered patches in various locations. An idea of which locations were most frequently affected, either alone or in conjunction with other parts, may be had from Table 2.

TABLE 2.—DISTRIBUTION OF LESIONS IN OTHER THAN GENERALIZED CASES

Part of Body	Alone		With Other Parts	
	Typical	Hypertrophic	Typical	Hypertrophic
Mouth	7	..	10	..
Face	4	..	6	..
Neck	4	..	17	..
Arms	8	1	53	2
Hands, wrists...	5	3	26	2
Trunk	3	..	20	2
Thighs, buttocks	3	..	12	1
Penis	1	..	4	..
Scrotum	..	..	1	..
Anus	..	..	2	..
Legs	10	9	3	30
Feet	..	..	8	1
Fingernails	..	..	1	..

It will be noted in these figures that, though the arms and hands are by far the most frequently affected, all parts of the body are liable to the disease. The hypertrophic variety is most often seen on the lower extremities though occasionally other parts are affected.

VARIATIONS IN TYPE

Numerous peculiarities were seen in the localized cases. A few were linear and seemed to follow the course of certain nerves while two linear cases showed a moniliform arrangement. These linear cases were so few in number as to have no particular significance.

There were rather frequent examples of the circinate and annular type of lesions, which were composed of slightly hypertrophic papules but did not differ in other respects from the ordinary cases.

Six cases showed small or medium sized vesicles, as well as papules, and in two cases these vesicles were located on the soles.

Fig. 1.—Bullous lichen planus.

One case (Fig. 1) had several crops of large bullae, chiefly on the thighs and arms, while another showed bullae on the arms and neck.

The single case of involvement of the nail showed a scaly brownish line several millimeters wide which extended along the midline of the thumb nail.

Another patient (Fig. 2) showed on the thighs a number of well-marked plane papules in and around typical plaques of pityriasis

rosea. The lichen planus lesions had been present for some time when the acute outbreak of pityriasis rosea occurred.

The lesions in the mouth varied in size from that of a pinhead papule to elevated plaques covering large areas of the cheeks or tongue. Figure 3 shows some lesions on the buccal mucosa located among very pronounced lesions of Fordyce's disease.

DISCUSSION

A careful study of the more complete histories of this series gives practically no positive evidence as to either the nervous or infectious origin of this condition and any interpretation of the cases is most

Fig. 2.—Pityriasis rosea and lichen planus.

difficult. In a small number of cases severe nervous shocks occurred before the eruption, but these were so few in number that they can be considered as coincidences. Other patients denied any possibility of nervous shock or worry of any kind. Drs. Engman and Mook in a previous publication have reported some of these cases and have also mentioned several other cases of this series that seem to show the infective character of the disease. In their discussion they also bring out the fact that many of the patients have distinct constitutional symptoms and are far more nervous and irritable than the pruritus would warrant. They believe that this may be a sign of a generalized

infective process of which the eruption is the outward manifestation. In this light it may be interesting to compare some characteristics of lichen planus with a number of definitely toxic or microbic conditions.

A number of these cases show a beginning in a primary single lesion and some in a single small patch of lesions. The general eruption appeared only after a varying incubation period. A few of these cases showed toxemic symptoms accompanying the rash. These characteristics are comparable to the primary and early manifestations of syphilis. The old hypertrophic lesions which remain long after the acute attack subsides are to a certain degree comparable to late manifestations of syphilis, while the response of both conditions to arsenic and mercury is quite striking. The appearance of lesions at points of irritation is another well known characteristic of lichen planus which is also present in a number of diseases that are definitely

Fig. 3.—Buccal lichen planus and Fordyce's disease.

toxemic or microbic in origin. Syphilis, erythema multiforme, dermatitis medicamentosa and the acute exanthems all show this characteristic. As all these conditions are indefinitely due to some toxin or micro-organism present in the blood stream, this similarity would seem to be of some significance. The histology of the lesion also suggests a microbic rather than a nervous process. All observers agree as to its granulomatous character. Its rather slow progress also seems to be more that of a microbic infection than a trophic disturbance.

It is hard to find a trophic disturbance producing a lesion with the histologic character of lichen planus. On the other hand, one can show lesions analogous to lichen planus caused by infection. The various clinical types of lesions in the lichen planus group may very well depend on the anatomic localization of the irritant (virus?). If it is follicular we have the accuminate lesion with the horny and ob-

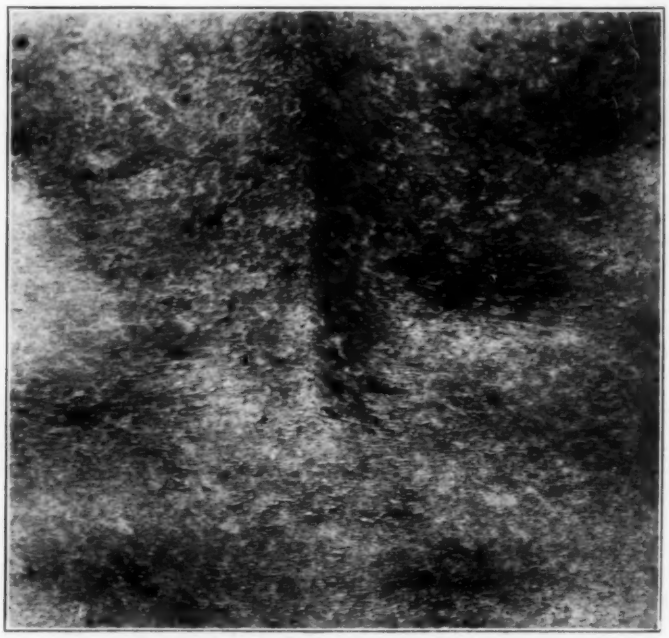

Fig. 4.—Circinate scars following lichen planus.

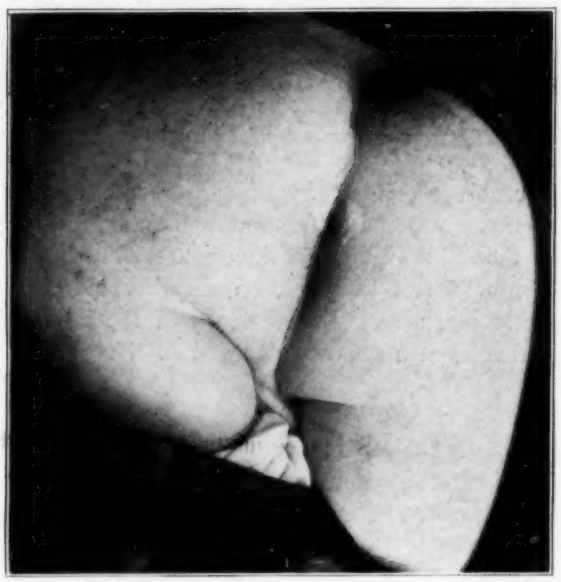

Fig. 5.—Lichen planus in a child 2 years old.

tuse papule. If it is in the upper part of the dermis without a localization particularly related to an anatomic structure, it may be a plain papule. Under certain unknown conditions horny concretions may occur about a follicular localization, producing umbilication when the horn is desquamated. The color, as in syphilis, depends on the localiza-

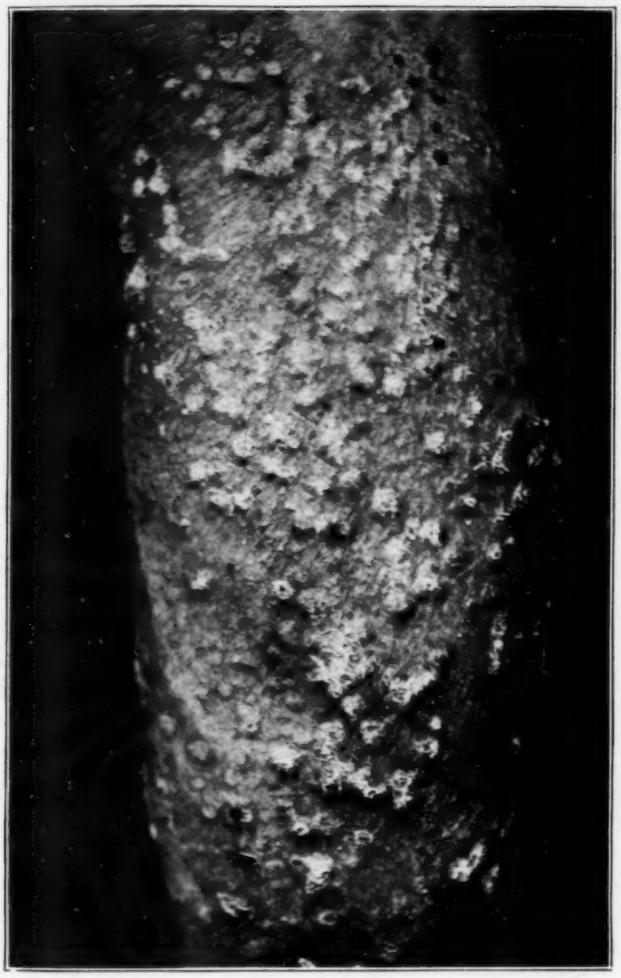

Fig. 6.—Marked hypertrophic lichen planus.

tion and the relative proportion of typical lichen planus cells. Patches are formed by the close localization of the virus (?) and by the fusing of groups. It must be remembered that lichen planus is a subepidermic-corium disease; the irritant or virus apparently finding a favorable habitat in the succulent lymph area just under the epidermis in the

upper part of the corium. Mild epithelial edema in this region is always a cause of pruritus. The hypertrophic lesion seems to be from histologic study a question of anatomic localization and soil, as some individuals seem to be prone to the hypertrophic form of lesion. The annular lesion, as in syphilis, can only be explained by the resistance of the tissues to the invasion of the virus, with rapid repair and peripheral extension of the proliferating invader. Sometimes restitutio ad integrum is not accomplished and superficial scars result, as in the atrophic type and in another type in which the skin seems to return to normal and regains its color except for leaving a minute cicatrix at the point of the former lesion (Fig. 4).

All of these points materially strengthen one's opinion of the microbic origin of the disease. The localization of the virus and the general symptoms of invasion in the acute cases cannot be analyzed on any other known etiologic basis; such conclusion conforms to the known and well demonstrated ideas of systemic invasion and cutaneous localization. Whether the hypothetic virus localizes in other organs than the skin has of course not been demonstrated, with the possible exception of the bladder and the gastro-intestinal canal.

TREATMENT

In the treatment, mercury, arsenic and the roentgen ray were found to be efficient. In acute cases mercuric chlorid, either intramuscularly or by mouth, worked well. The dose started at a moderate size and gradually increased. It was noted in many cases that the symptoms of nervousness and irritability and the pruritus disappeared under mercury, some time before the eruption was influenced. In the subacute cases the protiodid of mercury or Fowler's solution were used and in practically all of these, one or the other was found to effect a cure. In the chronic cases arsenic in the form of Asiatic pill was the most efficient remedy. Some few localized hypertrophic cases of long standing which could not be cleared with any of these remedies, responded to the roentgen ray. It was noted that though the preparations of arsenic mentioned were effective under the circumstances given, arsphenamin and its derivative were of little or no value in the treatment of lichen planus.

SPONTANEOUS GANGRENE FROM ENDARTERITIS-OBLITERANS *

AUGUSTUS RAVOGLI, M.D.

CINCINNATI

This disease occurred in a woman, 63 years of age, who had been married twice. The first husband died from aneurysm of the aorta abdominalis. During her first marriage she had had several miscarriages and one son who, at the age of 20, was tabetic. She enjoyed fairly good health until about six years ago when she had an ulcus perforans of the ball of the right foot and slight glycosuria. A mixed treatment and local application of a mercurial plaster caused the ulcer to heal, and she improved considerably. Last year she had an attack of acute pain in the foot and leg of the same side, and at the metatarsophalangeal joint a bluish spot formed, which in a few days turned into gangrene. The skin of the foot and leg was white, destitute of blood; the pulsation of the arteries, especially of the tibial, could scarcely be felt; no congestion and no phlebitis were present. The temperature of the skin of the foot and leg was below normal, the patient complaining of a cold sensation. Vision was greatly diminished in both eyes, the urine showed albumin and hyaline casts, together with some sugar. Fever, insomnia and mental depression, indicated that she was in a septicemic condition. The only hope of saving her life lay in amputation of the leg. After the operation she improved greatly, healing taking place by first intention.

Although the Wassermann test of the blood had been negative, she began treatment again with small doses of potassium iodid. From the stump a piece of the tibial artery was taken for pathologic examination.

The photomicrographs show the condition of the artery at the place of the formation of the thrombus. The intima is entirely deformed, and there is a tumor formed by small infiltrating cells in the middle of the lumen, where the blood has begun to coagulate. The artery below the thrombus is greatly deformed, the lumen is oblong with signs of canalization resulting from the efforts of Nature to force the blood through.

Apparently the rough edges of the broken intima act as factors causing the albumin and fibrin to coagulate and so to obstruct the

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* Read at the Forty-Third Annual Meeting of the American Dermatological Association, Asheville, N. C., April, 1920.

Fig. 1.—Tibial artery plugged with thrombus, a gummatous formation protruding from the media and affecting the intima; hard, thick thrombus occluding the lumen of the artery. There is a small hole on the side of the thrombus showing a tendency to canalization. (Low power.)

Fig. 2.—Tibial artery plugged with thrombus; a gummatous formation protruding from the media and affecting the intima; hard, thick thrombus occluding the lumen of the artery. There is a small hole on the side of the thrombus showing a tendency to canalization. (High power.)

Fig. 3.—This illustration shows the enormous infiltration between the connective tissues forming the walls of the artery with the proliferation of the connective tissue fibers. (High power.)

Fig. 4.—This illustration shows where the thrombus has had its origin from the breaking of the summit of the gummatous protuberance.

lumen of the bloood vessel. The whole process resembles a specific gumma which has broken the endothelium of the intima and so has produced the thrombus.

I therefore maintain that an endarteritis obliterans of specific origin exists.

Comparing the present case with thrombo-angiitis Buerger, we find that they are different conditions. Buerger's disease is a progressive one, increasing in gravity, showing more hydraulic alterations with redness, swelling, edema and plugged veins. It usually affects

Fig. 5.—The blood vessel taken quite a distance from the origin of the thrombus. It is entirely deformed in its lumen with a small opening showing the effort made by nature to force blood through the occluded vessel.

young persons, and apparently the immoderate use of tobacco is a factor. Buerger's disease comprehends a series of affections of the bloood and of the pressure of the blood vessels, which finally causes the formation of thrombus and gangrene. This condition can be benefited by intravenous infusion of Ringer's solution to dissolve the coagulated blood. In the present case of endarteritis obliterans, only the antisyphilitic remedies may give some relief, but there is no possibility of dissolving a hard coagulum formed from the damage of the intima by the specific gummatous process.

A FATAL CASE OF RECURRENT DESQUAMATIVE SCARLATINIFORM ERYTHEMA, WITH REVIEW OF THE SYMPTOMATOLOGY AND PROBABLE ETIOLOGY *

JOSEPH GRINDON, M.D.

ST. LOUIS

REPORT OF A CASE

History.—I saw the patient on January 31 and again the next day, in consultation with Dr. N. R. Rodes of Mexico, Mo. The patient was a large, strongly built blond of 17, a student at a military academy, where he boarded. The health of his family and his previous health were good. As far as could be learned, he had not been exposed to scarlet fever.

About the middle of November last, he "broke out red all over." He did not feel more than slightly ill. He had slight sore throat and moderate fever for about two days. The eruption lasted three days, and was immediately followed by profuse furfuraceous and lamellar scaling, the epidermis coming off from the palms in large strips. There were no sequelae. The attending physician made a diagnosis of scarlet fever.

He apparently remained in perfect health until January 18, when he had a second similar attack. His temperature was 102 for the first twenty-four hours; then it dropped to 99.5, returning to normal on the third day. There were no evening exacerbations. The pulse varied from 104 to 108. There was no albuminuria. There was general redness for forty-eight hours, followed as before by desquamation.

After an interval of nine days of apparent health, except for the scaling, he had a third eruption on January 29. His temperature was 101.6 to 103. On January 30 his temperature was 103 to 104; pulse, 120 to 140. His throat was much inflamed. No albuminuria was present. January 31 his temperature was 104 to 104.6.

Examination.—At the time of my visit, the face including the lips, neck, trunk, the upper extremities including the hands, the hips and thighs, showed a bright scarlatiniform redness. On the upper part of the legs, below the knees, the eruption was rather fine punctiform, in places coalescing into a continuous erythema. The feet were free from the eruption. The palms were deep red, due to exposure of the thinned epithelium by the last desquamation, which still persisted at the borders of the hands and at scattered points elsewhere. There were no hemorrhagic striae along the elbow-flexure folds, as pointed out in scarlet fever by Lippmann of St. Louis, but both above, and more particularly below the right elbow-flexure, there were crowded pinhead petechiae.

The mucous surfaces of the soft and hard palate, pharynx, fauces, tonsils and the buccal mucosae were deep red, velvety and swollen. The tonsillar crypts were not distended. The tongue was in part covered with a thick

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* Read at the Forty-Third Annual Meeting of the American Dermatological Association, Asheville, N. C., April, 1920.

white coat, through which showed the red fungiform papillae, as in scarlet fever, or, where this had become detached, it was smooth and bright red. There was throat pain only on attempting speech or deglutition, and even then the effort was more difficult than painful. The palpebral mucosae were deep red, the bulbar only slightly injected.

The lateral cervical lymph nodes were much enlarged. No other adenopathy was present. There was slight pain and tenderness about the elbows and other large joints. The bowels were slightly costive. Heart and lungs were negative. Mentality was clear.

Course of Disease.—The later history was communicated to me by Dr. Rodes. On February 1, the erythema grew lighter in hue, but again flared up for a day. On the third, jaundice appeared, which rapidly deepened, becoming quite intense. There was no nausea or vomiting, but tenderness developed over the liver and gallbladder, and became more marked over the joints. No albuminuria was present.

About midnight of the fourth, the patient became dyspneic, and from that time there was "a rapid intensifying of all mouth and throat symptoms, and intense swelling of the tongue and whole throat and neck." The dyspnea continued to recur in attacks of increasing severity, and at 2 p. m. of the fifth a surgeon, Dr. J. G. Moore, was called in to advise as to a tracheotomy.

Dr. Moore reports as follows: "At 2 p. m. the patient had extreme spasmodic dyspnea. The patient was very weak, jaundiced and evidently septic. The throat presented a sloughing appearance, but the examination was unsatisfactory, because of pain and exhaustion. The patient had just recovered from a severe attack of dyspnea. Tracheotomy was discussed, but delayed.

"At 5:30 p. m. the patient had another severe attack of dyspnea. Tracheotomy was attempted under local anesthesia. Breathing ceased under injection of procain. A rapid operation was performed, but artificial respiration proved ineffective. Some blood was found in the trachea. No membrane could be seen or felt in the larynx or trachea. Marked edema about the lower part of the larynx and vocal cords had almost obliterated the breathing space."

The following differential count was made by Dr. Jolley of Mexico on January 31: polymorphonuclears, 88 per cent.; small lymphocytes, 4 per cent.; large lymphocytes, 2 per cent.; granular eosinophils, 4 per cent.; myelocytes, 2 per cent. No postmortem examination was made.

The erythema in each attack began on the chest and arms.

LITERATURE ON THIS DISEASE

Cases of recurrent scarlatiniform erythema terminating fatally have been recorded, but in these, so far as I am aware, there were present other conditions amply accounting for death, while in this case fatality was directly due to lesions of the upper respiratory tract forming an integral part of the syndrome under consideration.

In Hallopeau and Tuffier's [1] fatal case there was rheumatism with pericarditis and albuminuria. Le Gendre's [2] post-typhoid case was not recurrent, and showed unhealed intestinal ulcers and a purulent tuber-

1. Hallopeau and Tuffier: Bull. et mém. Soc. méd. d. hôp. de Par., Series 2. **19**:221, 1882.

2. Le Gendre: Bull. et mém. Soc. méd. d. hôp. de Par., 1893.

culous focus in the lung. Devic and Gardère [3] report a fatal case in which, however, the erythema was evidently but a comparatively unimportant detail added to the grave conditions which determined death, namely, arterial thrombosis due to an infection consecutive on a quiescent lung tuberculosis. The data in this case as to temperature, pulse and general symptoms are consequently not included in the summary given in the second part of this paper.

In reading the various textbook articles on this affection, one finds agreement as to the chief features, but more or less divergence as to some of the accompanying symptoms, some authors denying the existence of phenomena mentioned by others, and some naming symptoms as absent or mild which others say are at times severe or grave. Evidently many of these descriptions are based on incomplete information, due to the fact that the data are only to be arrived at by careful study of numerous widely scattered case reports. Even after such study of a long list of cases, it is difficult to grasp or retain the variations in symptomatology. It seemed, therefore, desirable to digest further the matter by collating the various symptoms under their proper heads so as to show their relative incidence and therefore their diagnostic value.

I have also tried to present in condensed form what has seemed probable or has been surmised as to the etiology.

Most of the facts presented are only confirmatory of what is to be found in the excellent articles by Brocq, Besnier and Doyon, Elliot, Blanc, Whitehouse, Hartzell and others. A few moot points only remain to be settled.

It may be argued that single attacks of scarlatiniform erythema are not essentially different from those that recur. As limits must be set to such an article as this, however, even though arbitrary, this form of the disease is not considered. It also seemed proper to exclude cases in which each attack was preceded by the administration of a drug, such as quinin, as in Stelwagon's well-known case, or in the second case reported by Frank.[4] This was a case of dermatitis medicamentosa, and as such falls outside the scope of this paper. The same is true of Besnier and Doyon's [5] Cases 3 and 4. It seemed, however, proper to include cases in which a first attack, following the use of a drug, internal or external, were succeeded by recurrences without such apparent cause, or cases in which some recurrences followed the use of drugs, while others did not.

3. Devic and Gardère: Rev. d. méd. **31**:391 (April) 1911.
4. Frank: Jour. Cutan. & Genit.-Urin. Dis., 1897, p. 16.
5. Besnier and Doyon: Notes to Kaposi's Treatise, Vol. 2.

Gardiner's [6] case, with a single recurrence after ten years, and "very rapid pulse," seemed doubtful, and the details too meager. I similarly exclude a case of single recurrence after eleven years, observed by me, as I could not feel sure as to the true nature of the first attack. These differ too widely from the type, with its several or many recurrences at far briefer intervals, to fit easily into it. In an intermediate position stand certain cases quoted below in which a series of recurrences was broken by a long interval only to be again resumed.

One should distinguish between recurrences and relapses, a point not brought out, so far as I am aware, in systematic articles. It is quite usual for an interval of freedom lasting over several or many months to be followed by a series of attacks separated by days only, the erythema reappearing during the desquamation following the last attack.

There seems to be general agreement on the following points, namely, that the pulse is generally slow, showing "absence of the usual relations between pulse and temperature in scarlet fever";[7] that desquamation begins much earlier than in scarlet fever, generally before disappearance of the erythema (a number of writers insist on this as a cardinal diagnostic point); that "recurrences are frequent in youth, rare in adult life, and disappear with age,"[5] although Elliot [8] says that recurrences "tend to come at shorter intervals according to the duration of the disease"; that later attacks are, as a general rule, less grave than the earlier. The fatal case here reported forms a notable exception.

Of course the number of cases in which a certain symptom is mentioned does not show the proportionate incidence of that symptom, since many reporters omit mention of some symptoms. It serves, however, to bring that symptom into greater or less prominence.

COLLATION OF SYMPTOMS

Number and Distribution of Recurrences.—In one case there were three recurrences in two years;[9] in one case, seven recurrences in two years and another after an interval of three years;[9] in one case, two recurrences in six months;[9] in one case, seven recurrences in five years at intervals of from four to eight months;[4] in one case, four recurrences in five years;[10] in one case, three recurrences in two years and four months;[11] in one case, twenty-three recurrences in

6. Gardiner: Brit. Jour. Derm. **20**:245, 1908.
7. Blanc: Internat. Clinics, October, 1891.
8. Elliot: Med. Rec., 1891, p. 563.
9. Kramsztyk: Jahrb. f. Kinderheilk., 1902, p. 326.
10. Rotillon and Gougelet: Ann. de dermat. et syph., 1887.
11. Blanc: Jour. Cutan. & Gen.-Urin. Dis., 1893, p. 11.

eleven years and six months;[11] in one case six recurrences in one year;[5] in one case, four recurrences in two years;[12] in one case, seven recurrences in seven years;[5] in one case, five recurrences in two years and four months;[5] in one case thirteen recurrences in twenty-one months;[13] in one case, twenty recurrences;[14] in one case, 100 recurrences,[15] probably a "round number"; in one case, recurrences each spring and fall for seven years, then an eight year interval followed by another recurrence;[7] in one case, nine recurrences in four years and two months. The intervals in their order were five, two, seventeen, five, nine, one, five, four and two months. The seventh recurrence was followed by six relapses within a brief space;[16] in one case there were three recurrences in three years and eight months; the intervals were twelve, twelve and twenty months, with single relapses after the second and third recurrence.[8] In one case, four recurrences occurred in seven years and three months. The intervals were two years, four years, six months and nine months. The last recurrence was followed by two relapses.[7] In one case there were eight recurrences in two years.[17] In one case there were three recurrences in one year.[18]

Two cases are so extraordinary as to deserve repetition. Sligh[19] reports "Each year since infancy (thirty-six years), on the twenty-fourth day of July the patient has been taken ill, and within a few days thereafter, has shed the skin from the entire surface of his body, including the finger and toe nails." This occurred between 3 and 9 p. m., the acute stage lasting four or five hours. The skin came off two to four days later. Dr. Sligh observed the patient through one of these attacks. The other case, Frank's[20] recurred every year at the same date, between the ages of 7 and 33. These two cases strongly suggest a relation with the dates of flowering of plants furnishing a pollen to which the patients had become sensitized.

Intervals separating relapses (not recurrences): One week.[21] Each of four recurrences was followed by a relapse just before com-

12. Allen: Jour. Cutan. & Gen.-Urin. Dis., 1894, p. 169.
13. Whitehouse: Twentieth Century Practice, Vol. 5.
14. Besnier and Doyon: Soc. franç. de dermat. et syph., 1895.
15. Fox, Tilbury: Diseases of the Skin, p. 258.
16. Elliot: New York M. J., 1890, p. 29.
17. Richardière: Ann. de dermat. et syph. 4:338.
18. Petrini: Internat. Cong. de dermat. et syph., Paris, 1889.
19. Sligh: Internat. Med. Mag., June, 1893, p. 463.
20. Frank: West. M. Reporter, 1891, p. 37.
21. Billet: Bull. et mém. Soc. méd. d. hôp. de Par., April 11, 1902.

pletion of desquamation.[4] Nineteen days.[11] Three relapses within one month.[5] Seven relapses in five months.[10] A relapse within two weeks.[7]

Duration of erythema: One to six days;[22] three days;[8] four days;[7] first attack four days;[23] first four days, later one to three;[16] three days, in another case six days;[9] generally five or six days;[13] about ten days.[12]

Day of Beginning Desquamation.—Desquamation usually begins on the second or third day;[24] second or fourth day;[25] third or fourth day.[26] Desquamation usually begins before the rash has faded, say almost all who refer to this point, two noticeable exceptions being a case of Kramsztyk's [9] in which it came on only a week after the appearance of the rash, and one of Blanc's [7] in which it was delayed until "some time after the subsidence of the rash."

Duration of Desquamation.—One case lasted two, and one three weeks; the average is two to six weeks;[5] one case, two to three weeks, "many last a week or two, but more often it ceases gradually in from three weeks to two months,"[13] three to four weeks [16] or four weeks.[7]

Site of first manifestation: face; neck, upper chest;[11] one case neck, one thighs;[5] chest;[16] chest and hands;[8] some part of trunk;[27] in one case, flexures. Other writers say that first manifestations "may appear anywhere, usually not on the face;"[13] "no precise point of election."[5]

Distribution of Eruption.—In most reports in which the point is noted, the rash became universal, the feet perhaps most frequently escaping. Per contra may be placed the following: "The first attack was universal, but all subsequent ones were limited to the hands and feet."[22] "Numerous outbreaks limited to the hands and feet;[24] occasionally localized, so remaining, and ever retaining the same distribution in recurrences."[5]

Various writers note the presence of miliary vesicles, just preceding or at the commencement of desquamation.

Punctate petechiae have been noted by some as occasionally present.[28]

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22. Elliot: Morrow's System, vol. 3.
23. Loviat: Jour. d. mal. cutan. et syph., 1894.
24. Bulkley: Arch. of Derm. **1**: 1878.
25. Frank: Jour. Cutan. & Gen.-Urin. Dis., 1897, p. 16. Besnier and Doyon (Footnote 5).
26. Whitehouse: Twentieth Century Practice, vol. 5. Elliot (Footnote 22).
27. Hartzell: Univ. Med. Mag., August, 1895.
28. Besnier and Doyon: Notes to Kaposi's Treatise, vol. 2. Whitehouse (Footnote 13). Elliot (Footnote 22).

Edema is sometimes seen,[29] rarely general, oftener localized,[13] as in the face,[11] and especially eyelids;[3] face and extremities.[10] Again its absence has been noted in some cases.[30]

Desquamation is sometimes accompanied by the fall of finger and toe nails;[31] while the fact of their remaining unaffected is sometimes noted.[13, 16]

Adenopathy about the head and neck was noted by Frank.[4]

Involvement of Mucous Membranes.—In this particular cases differ, as do the opinions of writers. In one of Kramsztyk's [9] patients the pharynx was uninvolved, and in the other it was reddened. Hartzell [27] says: "throat symptoms are absent or very mild." Whitehouse [13] says the throat is only slightly reddened and not swollen. Stelwagon [32] says: "the swollen fauces of scarlet fever are wanting." Besnier and Doyon [5] state that the "gums and buccal mucous membrane are often red and swollen, later with exfoliation of macerated epithelium. The nasal and palpebral mucosae are often involved." Among reported cases one finds "mucous membranes normal in every way";[16] the soft palate showed a light erythematous blush in one case; in another case "the throat ached";[7] there was erythematous pharyngitis in one case and in another, slight sore throat; in another, moderate redness of the pharynx, ulcerative stomatitis and pain on swallowing;[5] redness of pharynx;[17] tongue, fauces and pharynx showed evidences of catarrhal inflammation;[4] the mucous membrane of the roof of the mouth exfoliated in a solid mass;[11] there were sore throat, cough and hoarseness.[5]

Tongue.—The tongue is red and peeled in some cases, as in Féréol's. It may be coated, red at the tip and edges, sometimes bright red.[5] "In my cases the tongue has several times been smooth as though denuded of epidermis."[22] It may at first be coated and later peel off, leaving it clean but not red.[11] The tongue may present minute papillae at its tip and edges, but is not of the true strawberry type.[13] Some authors (Kramsztyk,[9] Whitehouse,[13] Elliot,[22] Hartzell,[27] Stelwagon [32]) especially mention the absence of the strawberry tongue.

Kidney Lesions.—Hartzell [27] says there are no kidney symptoms. Kramsztyk,[9] in three cases, reports "no visceral lesions." Frank [4] says that the absence of albuminuria is a distinguishing character. Absence of albumin is noted in a number of reports by Besnier and Doyon

29. Besnier and Doyon: Notes to Kaposi's Treatise, vol. 2. Elliot (Footnote 22).

30. Blanc: International Clinics, October, 1871. Elliot (Footnote 16).

31. Blanc: International Clinics, October, 1891; Richardière (Footnote 17); Frank (Footnote 20); Elliot (Footnote 22).

32. Stelwagon: Diseases of the Skin, Philadelphia, W. B. Saunders Company, Ed. 8, p. 156.

(eleven cases)[5] and others (Frank,[4] Blanc,[7] Rotillon and Gougelet,[10] Blanc,[11] Allen,[12] Elliot[16] Other authors (Rossigneux,[36] Perret[33]) note its presence. It was present in Hallopeau and Tuffier's fatal case but, as before stated, it was doubtless independent of the erythema. Elliot[22] says; "Occasionally albumin may be found in the urine though it will be difficult to decide whether it is due to the erythema, or whether preexisting, or the result of some other cause." The problem just stated may at times find an answer as indicated by Devic and Gardère,[3] "One can hardly affirm that it (albuminuria) bears no relation to this affection, when it has been seen to appear with the erythema, only again to disappear." Unfortunately they furnish no references on this most essential point. In one of Whitehouse's[13] cases severe hematuria preceded each attack.

Joint Involvement.—Authors mention "arthralgia and arthropathies,"[22] pain in the back, hip and knees,[7] and joint pains.[34]

Pulmonary, cardiac and pericardial affections[35] are probably only incidentally present.

Prodromes—These are apparently generally absent, although there are a few observations to the contrary. Thus the eruption has been "preceded by chills, nervousness, melancholia, dizziness and excessive sweating".[16] It has been preceded for several days by chills and fever, headache and itching of the chest and hands,[8] malaise for a day or two, then fever, headache and itching for forty-eight hours;[7] "vomiting, nervousness, restlessness, and tingling of the surface for a few days".[19]

General Symptoms.—These are generally slight, but occasionally severe: dull fever and headache were present in eleven cases;[5] headache and light fever;[7] vomiting and fever;[20] dizziness, headache, nausea and vomiting[11] are sometimes present. On the other hand, we have "symptoms of typhoid" (Féréol, quoted by Besnier and Doyon).[5] Frank says there is a condition of deep depression and exhaustion; the pulse is low and active stimulation has to be resorted to.

Pulse and Temperature.—Besnier and Doyon[5] state that "fever is almost always present, but varies widely in different cases, exceptionally it is absent." In one case it rose to 104.9. They quote Rayer, who records 100.4 and 107.6, adding that "they make a mental reservation as to the last figure, but that it at least shows the clinical use of the thermometer at the beginning of the nineteenth century."

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33. Perret: Lyon méd., 1885.

34. Besnier and Doyon: Notes to Kaposi's Treatise, vol. 2; Rotillon and Gougelet: Ann. de dermat. et syph., 1887.

35. Devic and Gardère: Rev. d. méd., April, 1911. Elliot (Footnote 22).

36. Rossigneux: Lyon méd., 1892.

The highest temperatures recorded in each case with the accompanying pulse rate are: temperature 99.8, pulse 98;[11] temperature 100, pulse 90;[16] temperature 102, in another case 103, pulse 100;[7] temperature 103, pulse 88.[20] In two infants observed the temperature was 103.4, pulse 174, and temperature 105.6, pulse 144.[9] One case showed in the first attack a temperature of 104, and in the fourth attack, a temperature of 103, pulse 120;[4] another a temperature of 105.8.[13]

Etiology.—One must almost of necessity look for a toxic cause for these phenomena. It seems equally certain that this may be any one of a widely varying series of causes. There is in no single instance anything more than a certain degree of probability as to the existence of a causal relation. It is only the absence of any constant factor, unless it be a predisposition, or condition of ready sensitization, that lends any significance to the following list of surmised causes.

Rheumatism stands out preeminently: "articular rheumatism and endocardial lesions";[10] "frequently in connection with rheumatism";[22] "acute articular rheumatism"; "rheumatic patient suffering from sciatica" (quoted from Bondet [33]); rheumatism with pericarditis.[1] Other infections are: "first attack after convalescence from puerperal fever, later repeated attacks without any assignable causes";[23] infected wound of finger;[16] true scarlet fever, two cases, and true scarlet fever and measles, one case;[9] malaria, organism found;[21] "in the ague of young children, showing the same tendency to periodic return as is seen in intermittent fever" (Cheadle, quoted by Elliot).[22] "Each recurrence preceded painful menstruation by a day or two;" in another, "at every menstrual epoch." There was an enlarged and prolapsed ovary.[16] Intermediate between this condition and dermatitis medicamentosa, and possibly pointing to a fundamental identity, is a case in which some attacks occurred after taking antipyrin or cryogen, while others were "spontaneous."[3] Both internal and external causes may be concerned in the same case, as when the first attack followed rhus dermatitis, and the second and fourth tonsillitis.[4] Among external causes are mentioned, suddenly checked perspiration;[11] chilling of surface (eleven cases);[5] cold baths (Vogler, quoted by Elliott).[16]

The variety of possible causes is emphasized by many: "Such eruptions have been seen to develop under the most various influences from the most divergent causes".[16] "Accidents precipitating the attack differ in each case".[11] Other authors say that the cause often remains undiscovered, "without any definite exciting cause";[37] "some in which the causative influence could not be determined."[16]

37. Besnier and Doyon: Soc. franç. de derm. et syph., 1895.

CONCLUSIONS

1. Recurrences separated by several or many months are often followed by one, or a series of relapses at intervals of a few days only.

2. The rash usually lasts three or four days, exceptionally a week or more.

3. Desquamation begins oftenest in three days, and continues two to three weeks, rarely longer. It is sometimes accompanied by falling of the nails.

4. Edema is often present, miliary vesicles sometimes, petechiae more rarely.

5. The upper respiratory mucosae are generally mildly, and rarely severely, involved. The tongue is generally coated, later peeling and red. The strawberry tongue observed in this case has not hitherto been recorded.

5. Albuminuria is rarely if ever present, unless due to some independent condition. It is possible that it may exceptionally occur.

7. The large joints are sometimes mildly involved.

8. Prodromes, febrile, gastric and nervous, continuing for a few hours or days, are present in a minority of cases.

9. General symptoms, similar to those of the prodromes, always accompany the rash. They are generally mild, but occasionally severe.

10. Fever is present at least part of the time, but is rarely high.

11. The pulse is never disproportionately high, as in scarlet fever.

12. The only constant etiologic factor lies in individual predisposition. Assigned exciting causes, covering a wide range, have oftenest been septic or toxic, although in some cases no such cause has been discovered. External causes seem occasionally to be implicated.

13. Symptoms forming an integrating part of the syndrome constituting recurrent desquamative scarlatiniform erythema may exceptionally be grave or even fatal.

DISCUSSION

DR. TOWLE said that as he listened to Dr. Grindon's paper he was strongly reminded of the cases that were once called "surgical scarlet fever." They started with a wound, and developed a rash that spread outward, and there might be recurrences or a reinfection. Other cases, he had read, were due to focal infection in the sense that there was an abscess in the interior somewhere, with general toxemia.

These cases were also subject to recurrences and exacerbations. He wished Dr. Grindon had given a little more detail concerning the condition of the liver. In his opinion the symptoms pointed rather to a septic abscess in the liver producing the recurrent effects in the skin.

DR. HARTZELL thought there was little doubt but that under the term "recurrent scarlatiniform erythema" a number of diseases etiologically quite dissimilar were included. There was a group in which the symptoms were

largely confined to the skin without any constitutional symptoms worthy of mention. These cases recurred year after year. In a case reported by himself several years ago the patient had suffered many attacks and had been quarantined because of the diagnosis of scarlet fever. Cases of the kind reported by Dr. Grindon certainly were the result of a marked infection of some sort.

Dr. McEwen thought this paper called attention to something that dermatologists were prone to let pass, namely, the securing of necropsies. He felt that if Dr. Grindon's case had been posted the cause of the trouble would have been found in the gall tract.

Dr. Lane said that he had recently seen a child of 5 who had had six attacks of recurrent scarlatiniform erythema in nine months. He saw the patient in the last attack, and was surprised to find that the child had a typical strawberry tongue. This was seen in none of Dr. Grindon's cases and is usually not found in this disease, its presence being indicative of scarlet fever rather than of erythema scarlatiniform.

In this case it is quite likely that the cause might have been in the tonsils, as they were hypertrophied and chronically inflamed. The physician in attendance had repeatedly urged their removal without avail, therefore nothing could be said of the prophylactic effect of this procedure. It seemed likely, however, that this case should be included in the class referred to by Dr. Fordyce.

Dr. Wallhauser agreed with Dr. Hartzell and Dr. Fordyce that many different conditions were being considered under the head of erythema scarlatiniforme, which was an extremely rare condition.

Dr. Wallhauser reported a case and showed photographs taken during the seventeenth attack. The patient was a woman, 24 years of age, who had had recurring attacks over a period of about twenty years. The initial attack occurred at the age of 5; each recurrence had a distinct onset, consisting of a feeling of malaise and depression for about one week, during which time the patient became pale and sallow. The eruption appeared abruptly all over the body, including the extremities—the face became flushed with circumorbital pallor. The onset of the eruption was accompanied by chills, followed by a rise in temperature, usually to 104 or 105 degrees; nausea and vomiting occurred during the first days of the eruption, and in some attacks was a most distressing symptom; mild or severe throat symptoms were present and painful deglutition was continuous until the disappearance of the eruption; the tongue was heavily coated, but lacked the characteristic enlargement of the papillae seen in scarlet fever. The eruption began to fade on the fourth day with a subsidence of the constitutional symptoms. Desquamation occurred, and in some attacks was complete in ten or twelve days, while in others, it was more gradual, extending over a period of four or five weeks. The photograph of the hand, showing complete glove-like exfoliation was taken at the end of the third week of the eruption.

Dr. Engman stated that Dr. Grindon had told him of this case and had reported it before the St. Louis Dermatological Society. He considered the case instructive and interesting. In his opinion there should be two distinct groups; one a seasonal condition, which might be due to pollen or any condition that might occur in certain seasons, and the large group of conditions that were septic, or toxic, in which some toxin developed from food or microorganisms.

Dr. Engman was observing a patient who had had six attacks that had been diagnosed as scarlet fever. The patient was a boy 16 or 17 years old in whom the attacks could be produced at will by quinin, but at other times they had occurred without quinin. This was analogous to dermatitis herpetiformis, in which typical attacks could be produced at will by iodid of potassium, which histologically and clinically was dermatitis herpetiformis. It seemed in Dr. Grindon's case to be some septic process.

Dr. Grindon (closing), replying to Dr. Fordyce, said that the leukocyte count was above 8,000.

The implication of the liver in this case was clear, but apparently this was not the cause of the trouble but a result. The patient was apparently in perfect health between his three attacks, and it was only after the last attack had existed for several days that any symptom developed to attract attention to the liver, such as enlargement, pain or jaundice. It was to be regretted that there had been no postmortem examination. The patient was a hundred miles from St. Louis and the local physicians were unable to secure a postmortem examination. This was, perhaps, partly due to the fact that Dr. Grindon, unfortunately, had said it was a condition with which the profession was quite familiar; that it was never fatal; and that the patient would do well.

As was so truly said by Dr. Hartzell, we are dealing with a group or syndrome, and not with a disease, etiologically; but as Dr. Wallhauser said, a condition in which there are etiologic differences, but which clinically remains true to type. It constitutes at least a clinical entity. Constancy in the duration of the erythema, in the date of beginning desquamation, and in the relation of pulse to temperature, make it useful to class these cases together and to study them under one head until more is known about them.

In studying reports of the cases and trying to separate them into groups he found a rarely broken agreement of symptoms. One thing that stands out is the distinction between recurrences and relapses. In this case there was an interval of apparent perfect health for ten weeks between the first and second attacks, so that it was difficult to believe that the same septic cause was active throughout that time. However, Dr. Grindon believed that there was a septic cause.

He was interested in hearing Dr. Lane's observation as to the strawberry tongue. So far as he could learn, this had not been recorded in any other case except the one forming the subject of this report.

The point that to him seemed diagnostic in the first attack was the absence of the characteristic disproportion between pulse and temperature so familiar in scarlet fever.

SYPHILITIC INFECTION OF THE CENTRAL NERVOUS SYSTEM OF THE RABBIT*

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Since it was first shown that rabbits were susceptible to infection with *Spirochaeta pallida*, numerous attempts have been made to devise means of producing an infection of the central nervous system in these animals which might be utilized in studying this phase of human syphilis. For the most part, the experiments which have been carried out appear to have been based on the assumption that this could not be accomplished by a simple testicular or scrotal inoculation, but that it was necessary to resort to some intensive form of inoculation, such as an intravenous, intracardial or intracranial inoculation or to the use of repeated inoculations of various kinds. This idea may be accounted for in part by the use of recently isolated strains of *Spirochaeta pallida* and in part by the apparent inability to produce a generalized disease in the rabbits by ordinary methods of inoculation.

How successful these efforts have proved it is difficult to say. The evidence of infection which has been submitted in cases other than those of direct inoculation into the cerebrospinal canal has consisted largely in the demonstration of lesions which, although analogous to certain lesions observed in man, might be produced by a variety of causes and are frequently found in rabbits which have not been inoculated with *Spirochaeta pallida*. The significance of the lesions described, therefore, has remained somewhat uncertain.

It appeared to us that, since a widespread dissemination of spirochetes always occurred in rabbits inoculated in the testicles or scrotum, whether lesions developed elsewhere or not, the first thing to be determined as an approach to the study of infections of the central nervous system was whether or not the organisms gained access to the cerebrospinal canal in ordinary types of infection and second, whether the same influences which control processes of infection in other parts of the body might not extend also to localization of the organisms in the central nervous system.

It was obvious also that the first essential in attempting to determine these facts was the use of a strain of *Spirochaeta pallida* which was as well adapted to the rabbit as possible.

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Accordingly, a small series of experiments was undertaken, the purpose of which was to determine the presence or absence of *Spirochaeta pallida* in the central nervous system at various periods of the experimental infection, more as a means of orientation than as an attempt to solve any particular problem. However, the results of these experiments throw considerable light on infection of the central nervous system in the rabbit, and for that reason may be reported in brief.

EXPERIMENTAL PRODUCTION OF SYPHILIS

The method of procedure was to obtain cerebrospinal fluid from infected animals as free from contamination with blood or tissue juices as possible and to determine the presence of spirochetes by injecting this fluid into the testicles of normal rabbits. To accomplish this, the animal was killed with ether and bled from the heart to relieve the congestion of the meningeal and other vessels. The tissues over the occipito-atlantoid membrane were then removed and the membrane scraped clean, after which a needle was inserted through the membrane and the fluid removed in fractional amounts by suction with a small syringe. In this way, an average of 0.6 to 0.8 c.c. of fluid could be obtained which was free from any visible contamination with blood.

The fluid thus obtained was examined microscopically and injected into one testicle of one or two normal rabbits, depending on the amount of fluid available. These animals were then kept under observation for a period of sixty days for the purpose of determining an infection in the testicle.

The spinal fluid of thirteen rabbits that had been inoculated in the testicles was examined by this method. Nine of these rabbits were infected with Nichols' strain of *Spirochaeta pallida* which was isolated from the cerebrospinal fluid of a neurorecidive in 1912 and four of them with an organism isolated from a mucous patch by Zinsser and Hopkins in 1913.

RESULTS

The Demonstration of Spirochetes.—The first series of animals examined consisted of five rabbits with early testicular infections. The fluid from one of these produced an orchitis after an incubation period of forty-three days in one of the two animals inoculated. Subinoculations from the others were all negative at the end of sixty days.

The successful transfer in this case came from an animal with an orchitis of eight days' duration which was produced by the Nichols strain of *Spirochaeta pallida.* There were large and actively progressing lesions in both testicles but no lesions elsewhere.

A second series of inoculations was then made from three rabbits with actively progressing generalized lesions. These gave two positive results. In one case, infection was again obtained in only one of the two subinoculations, while in the other, only one test animal was used.

One of the animals in which infection of the nervous system was proved had marked periosteal lesions with extensive necrosis of the nasal bones, which suggests the possibility of invasion of the central nervous system by way of the lymphatics. This animal was inoculated in both testicles with the Zinsser-Hopkins strain of *Spirochaeta pallida*, and the development of generalized lesions was induced by castration.

It is important to note that the incubation period of the infection produced by the spinal fluid of this animal was only thirty-six days, which is reasonably close to that of an infection produced by an inoculation with 0.5 c.c. of heavily infected blood or with an emulsion from an infected lymph node.

The other animal was inoculated in one testicle with the Nichols strain of *Spirochaeta pallida* and subsequently given a dose of 5 mg. per kilo of arsenophenyglycyl dichloro-m-aminophenol as a means of suppressing the testicular reaction. Generalized lesions were just beginning to appear and there were slight lesions of the nasal splints when the animal developed signs of a meningitis. Although the spinal fluid contained an increased number of cells, it was clear and no spirochetes could be demonstrated by dark field examination. At necropsy, no abnormality of the brain or cord could be detected beyond a possible injection of the meningeal vessels and a slight clouding of certain areas of the meninges.

The exact incubation period of the infection produced with this fluid cannot be given. The lesion in the testicle was first discovered forty-two days after inoculation, but it was then a well developed lesion of at least three or four days' duration.

The third group of animals whose spinal fluid was examined was composed of five rabbits, all of which had developed generalized lesions. At the time the examinations were made, these lesions were either regressing or had completely disappeared so that this group of cases might be classed under the head of inactive or latent infections. Inoculations from all of these animals gave negative results.

Alterations in the Spinal Fluid.—In addition to the demonstration of spirochetes in the cerebrospinal fluid of three animals, mention should also be made of the occurrence of certain obvious abnormalities in the fluid of animals when no active infection could be proved.

The striking features of these changes consisted in a slight clouding of the fluid and the presence of flocculi which on microscopic examination proved to be due to an increased number of cells and the formation of aggregates of cells and granular detritus.

These conditions were practically constant in the animals of group three, which suggests an antecedent infection in these cases with a subsequent disappearance of the spirochetes such as occurs during remissions in other forms of localized infection. This possibility is supported by the apparent frequency with which spirochetes were demonstrated during an active period of infections of an analogous character.

CONCLUSIONS

This series of experiments, although too limited to warrant any broad generalizations in regard to syphilitic infection of the central nervous system, is sufficient to show that such infections may be produced in the rabbit by an ordinary testicular inoculation of well adapted strains of *Spirochaeta pallida,* and that spirochetes may invade the central nervous system at a very early period of the infection.

How often this occurs is impossible to say since the methods used are subject to obvious limitations both as regards the type of infection which may be demonstrated in this way and the activity of the infection at the time the examination is made.

From this small series of experiments, it would appear, however, that invasion of the central nervous system by *Spirochaeta pallida* and the development of localized lesions are subject to the operation of the same set of conditions as are concerned in the occurrence of other manifestations of a generalized infection, and that by taking advantage of these conditions, it should be possible to favor this form of infection so as to increase both the incidence and severity of central nervous system involvement.

THE VANISHING LESION: A NEW PROBLEM IN TEACHING*

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BOSTON

Methods in teaching are not entirely beyond the influence of fashion. Changes occur in various courses that indicate the emphasis of a particular period. Class exercises give way to section teaching, with the advantage that students come in more intimate contact with both instructor and patient. Not long ago the didactic lecture seemed to be in peril of extinction. The teaching of syphilis has followed the general plan more or less closely. However, we still have a few didactic lectures and clinical exercises for the class; but the bulk of instruction is with small sections at the hospital.

Recently a new condition is confronting us: the vanishing lesions. The teacher of clinical syphilis must regard this changing condition with real apprehension. One no longer sees in the clinic the array of active lesions, both early and late, that were formerly available for teaching purposes. This condition is due largely to four causes: (1) early diagnosis; (2) better treatment (earlier and with arsphenamin); (3) prohibition, and (4) education.

Diagnosis is greatly facilitated by the state and municipal laboratories, in which the clinical findings or suspicions are verified by dark field examination and the Wassermann test. Arsphenamin is now within the reach of all. National prohibition will unquestionably diminish the number of primary lesions, and the free discussion of syphilis outside of medical meetings has caused many an old syphilitic patient to try to check up his physical condition by at least a Wassermann reaction, and many put themselves under treatment.

CLINICAL INSTRUCTION BASED ON PATIENT WITH SYPHILITIC LESIONS

The syphilitic patient with lesions is the real foundation of clinical instruction—not only for medical students and practitioners, dental students, and nurses; but also for the numerous agencies with their corps of workers who are turning to us for help and instruction, both medical and social; for syphilis, sooner or later, presents problems to all the agencies engaged in social betterment.

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*Read at the Forty-Third Annual Meeting of the American Dermatological Association, Asheville, N. C., April, 1920.

The growing practice of having a special department for the treatment of all stages and manifestations of both acquired and congenital syphilis has given the syphilographer a much wider scope of usefulness in the community. This condition is most gratifying. At the Massachusetts General Hospital we are in more or less intimate touch with about 160 different agencies or institutions, ranging from the municipal court with its probation officers, and the county jail, on the one hand, to the Bethesda Society (for the care of girls), the Children's Mission to Children, The Girls' Parole Department of the State, The State Department of Public Welfare, the Massachusetts Charitable Eye and Ear Infirmary, the Prenatal Clinic of the Boston Lying-in-Hospital, etc. Each has its own particular line of problems, but there is the same underlying cause as a meeting ground of common interest to us.

A society for the care of girls has recently arranged that all applicants for admission shall come to us for a complete physical examination, which includes a blood Wassermann test on all and a lumbar puncture when indicated. The two questions of gonorrhea and feeblemindedness are determined elsewhere. All the applicants have had some sexual experience. The advantages of a similar arrangement with the child-placing agencies is readily seen. It happens far too often that an apparently healthy baby with congenital syphilis is legally adopted, and the later syphilitic manifestations of eye, throat, or brain fall as a heavy burden on the foster parents.

The use of arsphenamin early in pregnancy has a pronounced effect on the viability and health of the fetus, so that many babies of syphilitic parents appear normal at birth. Such infants should be looked on as potentially syphilitic, and need most careful observation, or intelligent treatment, for an indefinite period. It is much harder to obtain the necessary co-operation from parents and attendants of these children when they show few or no signs of their congenital disease than when active lesions are present. It is also much more difficult to have precautions against infection carried out when there is no obvious reason for such a course.

Without the presence of infectious lesions it is difficult to teach the physicians and nurses in the public health courses. Syphilis then appears a benign infection. Practically the only lesions that are now available for demonstration are the ones new patients and occasional ward patients may show. The progress of repair in healing lesions may be of interest to the physician, but is of little teaching value. We all recall the days when especially typical cases were "booked up" for demonstrations several weeks in advance, without the least danger of treatment materially changing the character of the lesions.

The lack of material is especially felt in our work with the dental students, in whose instruction lesions in the mouth and throat, or about the face, are especially desired. One cannot assume the responsibility of the danger of contagion to associates by withholding arsphenamin from patients with infectious cases; and if arsphenamin is given, the desired patches are promptly healed. A recent house officer remarked that he had not seen over a dozen good examples of mucous lesions of the mouth during his two months' service in the department, with an average daily attendance of over a hundred patients.

It seems highly probable that the whole plan of teaching syphilids and the early infectious lesions may have to be changed, perhaps transferred from the out-patient to the wards, relying no more on ambulatory patients, but carrying out bedside instruction. Arrangements should be made for both teaching and isolation. Patients with infectious diseases that enter the ward now remain about ten days or two weeks, at which time they are returned to their homes with infectious lesions healed and only slight risk to their families. Their stay in the hospital has an educational value. These patients require less following up than patients that have not been in the ward. It is also easier for these patients to get leave from their employers to come for subsequent treatment.

At present there are about thirty beds available for infectious syphilitic patients in all the Boston hospitals combined, and throughout the state a large majority of the hospitals, both public and private, are still closed to syphilitic patients, either by custom, prejudice or the articles of incorporation. The infirmary of the state almshouse at Tewksbury has a considerable number of cases with demonstrable lesions most of the time, but the distance from the medical school is too great for its use as a teaching clinic under present conditions.

Several years ago surveys were made, in various clinics, to determine the number of hospital visits made by each patient with syphilis, and the results showed conclusively that most patients were simply treating symptoms, making no real attack on their disease. Of course relapses occurred. The introduction into the clinic of social service workers and a clinic secretary, with an adequate follow-up system, has already made a material improvement in these conditions. There are comparatively few patients now who do not receive at least one course of between six and eight arsphenamin injections, followed by a series of from twelve to fifteen gray oil injections, while many patients continue treatment until they are clinically and serologically cured. Under the present Massachusetts law, infectious syphilitic patients who lapse treatment for six weeks are reportable to the state board of health by name and residence. Then the state board notifies the local board, and the local board exerts the pressure necessary to

bring the patient under treatment again. Through this means about 25 per cent. of these delinquents have been returned to the clinic.

From the therapeutic standpoint the vanishing lesion is most encouraging, but to those who feel that syphilis is still a disease that should be diagnosed by the clinical signs and checked up by the laboratory, rather than left entirely for its diagnosis to the serologist, the outlook is not reassuring. Thirty years ago we were told in our course on public health that, owing to the protective power of vaccination, probably none of us would ever see a case of small-pox. In general medicine today there is said to be insufficient material for the clinical teaching of typhoid fever; and I recently heard an internist say that steps should be taken to have a few cases of pulmonary tuberculosis once more cared for in the wards of the general hospital, that they might be used for teaching purposes.

PHYSICIANS RECOGNIZE SYPHILIS LESS READILY

With a decreasing opportunity for observing primary lesions and the early syphilids, the medical profession as a whole will become still less acute in recognizing syphilis, especially extragenital infections situated in unusual places and, as a result, small epidemics of (innocent) inoculations (like the one from kissing reported by Dr. Schamberg a few years ago) are likely to occur more frequently.

Within a year I have seen three cases in which the primary sore was excised by a competent surgeon for a supposed malignant growth (inside of cheek, lip and tongue). This is not said in criticism, but simply by way of emphasis. If competent surgeons are doing such things, how many more cases are being unrecognized by the members of our profession who, for one reason or another, are less well trained? There is a constant need of remembering to consider the possibility of syphilis in all "cold sores," lesions of tongue, tonsils or eyelids, which last over two weeks and thereby differ in character from the ordinary benign lesions. The hardness, painlessness, and accompanying enlarged glands, which appear early, should always suggest primary syphilis.

It is common knowledge that most of the primary lesions on the hands or fingers are found with those who care for the sick (physicians, nurses, dentists, etc.); yet, knowing this, what is so rare as the early diagnosis of a doctor's digital chancre? These cases are always maltreated by deep incisions, curetting and poulticings; and the diagnosis is often made only when a secondary eruption presents itself, or a positive blood Wassermann reaction is obtained. Often from three to six months have elapsed since the infection occurred, during which time the wife usually has contracted the disease. Men who have

had good opportunities and should know primary syphilis failed to recognize these primary lesions. What can be expected of physicians of the future if we have not sufficient clinical material to give the proper instruction?

Extragenital primary lesions are apparently on the increase. The old conceded 10 per cent. seems now too small by at least 2 or 3 per cent. (If this increase is confined to Boston, I shall be glad to know it.)

Failure to recognize late syphilis may do some slight injury, but is not to be compared with such an oversight during the early stages. Syphilids often develop under cover of some other skin disease, such as scabies; and there have been several cases of extragenital infection of tongue, lip, tonsil, etc., associated with influenza in the recent epidemics, the primary lesions being ignored medically and the subsequent eruptions considered due in some way to the influenza infection. How many more cases of unsuspected syphilis have they created? Only eternal vigilance and the constant thought of the possibility of syphilis can prevent overlooking extragenital chancres. A routine histologic examination of all specimens from tonsillectomies, especially in adults, would detect certain cases of tonsillar chancre. A general physical examination, or even an inspection of the skin, would have shown the diagnosis and prevented needless operations in other cases of primary chancre of the tonsil.

The author has no desire to precipitate a quarrel with operators on the throat, laryngologists and others; but the fact remains that probably more chancres of the tonsils have been removed without recognition than all other extragenital primary chancres combined. Moreover, many of the patients were operated on with the secondary rash showing, and often the immediate object of the tonsillectomy was to relieve the acute painless swelling (the satellite bubo) of the tonsil gland. Little wonder then that we see physicians with primary lesions of the finger, contracted by performing a tonsillectomy in which the fingernail was used to free the tonsil from its capsule or in the removal of adenoid tissue. If it were possible to demonstrate primary syphilis of the tonsil to every medical student and carry home the conviction of the frequency of this condition, fewer tonsils would be removed before the possibility of syphilis had been considered and excluded.

During the war many civil conditions were temporarily given a military rating; and syphilis was once more brought into prominence as a venereal disease. With such a classification in the army and the navy, there can be no just criticism; but to class all marital, congenital and extragenital syphilis of civilians as a venereal disease is unfortunate and unfair. I trust there may be a concerted action on the part of the medical profession to overcome this renewed impression

that syphilis and venereal disease are synonyms—in other words, that sin and syphilis are always inseparable.

During the past year an unusual number of undoubted early secondary syphilitic patients have been seen in whom the site of infection could not be determined in any way, there being absolutely no glandular enlargement or remains of a possible chancre. Is this to be the style of the future? Is the primary lesion also vanishing?

From a therapeutic point of view the outlook for the syphilitic was never more hopeful. Whether the present methods of treatment endure matters little, for they will be displaced by something better and perhaps be guided by more exact methods. The past decade and a half has seen the application of practically all our present methods of precision: dark field, roentgen ray, animal inoculation, cultivation of spirochetes, spinal and ventricular punctures and study of these fluids, together with the Wassermann reaction. These tests also will stand until replaced by something better.

The widespread use of arsphenamin is chiefly responsible for the scarcity of lesions. With a prompt recognition of primary syphilis and more general use of arsphenamin, subsequent lesions will be still more rare. This applies not only to skin and mucous lesions, but to those conditions occurring years after infection, some of which have quite recently been shown to be almost exclusively of syphilitic origin—aneurysm of the aorta and aortitis. We now believe that the foundation for these lesions, like the foundation for tabes and paresis, is laid during the early secondary stage of the disease. The same condition undoubtedly holds true for most of the visceral lesions and probably for many of the late skin outbreaks as well. Adequate treatment, given in the primary or early secondary stage, should practically eliminate all the subsequent lesions, thereby working a radical change in all fields of general and special medicine.

TEACHING SUBSTITUTES FOR SYPHILITIC LESIONS

What are the teaching succedanea for syphilitic lesions? Ordinary photographs are but poor helps, showing only the site, number and relative size of lesions that lose much of the instructive value by their lack of correct coloring. Few of the atlases of colored plates are of practical value. Water color paintings of skin lesions are expensive. Wax models are expensive, and impracticable for use in class exercises or with large sections. Our greatest hope would seem to be in the application of color photography. If this can become available, some of the threatened dangers will be overcome as far as the recognition of signs by sight are concerned. Nothing can ever supplant the knowledge of indurations to be gained by handling. Touch and appearances must be appreciated together.

To supply these teaching outfits seems a fitting undertaking for some of the philanthropists or foundations interested in the question of better teaching in our medical schools. Can a better use be found for some of the money available for improving teaching conditions in our medical schools than in producing and perfecting sets of colored negatives and wax models that can be utilized in teaching primary lesions, the skin eruptions or mucous lesions of syphilis? By preparing colored negatives or lantern slides in a central plant or factory, sets or collections could be supplied at a much lower cost than would be the case were each school to make its own, and the collection would be more nearly complete.

There is hardly another field in medicine in which failure to make a correct diagnosis carries such grave consequences, not only to the patient, but to the family and to the community. Failure to use prophylaxis against ophthalmia neonatorum is a punishable offense in Massachusetts, as is the failure to report such condition to the board of health, when it exists. Prosecutions have occurred. The injury to such a baby may indeed be great, but the failure to recognize that a baby has congenital syphilis often means the early death of the child, though not infrequently the child lives long enough to infect some of its attendants or family. Many of the primary lesions occurring about the face in adults are the result of fondling an unrecognized syphilitic baby. Only recently has syphilis been added to the list of reportable diseases in Massachusetts.

SUMMARY

It seems probable that secondary and tertiary lesions of syphilis will continue to occur less and less frequently. This serious problem in teaching must be anticipated and solved by:

1. Provision of sufficient beds to care for the acutely infectious cases that cannot be properly isolated at home.
2. The segregation of syphilitic patients into one department, in which the various phases of the disease can be studied and treated.
3. Collecting photographs of all lesions that can be shown by prints or lantern slides.
4. Applying (if possible) the color process of photography.
5. Wax models—moulages—utilized to a greater extent in European medical schools and hospitals than in America. A plea for their production and use here was made by Dr. Wallis at the last meeting of the American Medical Association. These models will always be expensive and therefore not freely available.

DISCUSSION

DR. WILE said that those who were engaged in teaching syphilis must be distinctly interested in Dr. Smith's paper. His experience had been the opposite

of Dr. Smith's and the amount of material they were seeing today was much greater than that they were seeing many years ago; he believed this was due to the fact that syphilis was being centralized in their department, where previously it was not. Dr. Wile believed that the Utopia of the elimination of syphilis—so desirable, of course, from the patient's standpoint and undesirable from the teaching standpoint—was yet far off.

In regard to syphilis, Dr. Wile felt that the material was just beginning to be properly used for the purpose of instruction.

If the condition described by Dr. Smith should become general, Dr. Wile felt that any other substitute for the human subject, whether it be the actual photograph or the colored photograph, would fall far short of satisfaction. He believed that the living subject, not only in syphilis but in any other disease, was the only practical and desirable way of teaching the clinical aspects of the disease, as far as undergraduate students were concerned.

Dr. Wende stated that from observations in Buffalo he could substantiate those of Dr. Smith of Boston. He found, as did Dr. Smith, that material for the practical clinical teaching of the skin manifestation of syphilis is growing less and less owing, in his opinion, to the widespread early use of arsphenamin. He believed that he is now seeing but one case of typical skin lesions to five formerly. During the last two or three years in his classes in the dental school he had been unable to demonstrate satisfactorily syphilitic mucous membrane mouth lesions because of the scarcity of their appearance in his clinic.

In regard to the technic in securing photographic reproductions, he felt that today the ordinary black and white photography gave the best results obtainable. He had made many attempts to use color photography since its inception, but found the results not so satisfactory. He had also for several years had photographs colored by competent artists but had always found that in applying the colors much of the important and essential detail was erased or at least befogged, especially in lantern slides. In order to secure detail in high relief he had always found flashlight very unsatisfactory, but long exposure in good natural light with small lens aperture had always given him the most satisfactory results. He stated that all his reproductions were so produced; however, he appreciated the great excellence of the reproductions exhibited by Drs. Fordyce and MacKee.

Dr. Irvine agreed with Dr. Smith in regard to the vanishing lesion of syphilis. He thought they saw about the same number of active lesions (but not the same percentage), but that was because of the increase in their material. It was not infrequent in a clinic of fifty to seventy-five patients a day to have not a single skin lesion from which to teach. He thought Dr. Smith's paper was timely and, as brought out by Dr. Stokes in his paper, one must teach all the manifestations of syphilis and not center on the cutaneous ones alone. As time goes on it will become more and more necessary to teach syphilis from all standpoints.

Dr. Grindon agreed with Dr. Wende regarding the superiority of black and white over other pictures for those who were already familiar with the lesion and the disease. These would unconsciously add the color element and picture to themselves the lesions. On the other hand, to the man who does not know the lesion and has to be taught, it does not carry a full and true impression, no matter how close a reader he may be. It was a fact that no reproduction, whether it be by color photography, moulages or anything else, can take the

place of the lesion on the living subject. Palpation was just as important as the use of the eye, but perhaps in the future one will have to choose from imperfect methods.

As to the actual condition confronting the profession at present, Dr. Grindon's teaching is done with material at the St. Louis City Hospital. While clinical material is diminishng, there is still enough for teaching purposes. However, he feared that the time was not far distant when they would experience a similar condition to the one now existing in Boston. Probably early treatment was not as systematically employed in St. Louis as in Boston. There might be a way out of the difficulty as it existed in St. Louis and other large centers, furnished by the out-clinics conducted by private charities or associations where the early treatment of syphilis is carried out, ofttimes in the evenings. So far as he knew, this material in his city had not been utilized. It might be a wise plan to transfer the greater part of the teaching of early syphilis to out-patient departments in which patients came with primary and early secondary lesions.

Dr. Howard Fox thought that too much emphasis had generally been placed on the value of colored photographs in portraying skin diseases. While high class colored photographs were, of course, of great value for teaching, the element of color was often of distinctly less value than the distribution, configuration and character of the lesions. Dr. Fox had recently been experimenting with a comparatively new method of illumination for photography, an electric lamp of 1,000 watts, with blue lamp and reflector. It was especially suitable for physicians having a small space available for photographic work and was a quick, clean and convenient method. It was best suited for localized areas of the body. One objection was the difficulty in avoiding a dark shadow on the background, as the rays of light were concentrated in contradistinction to the diffused character of daylight and flashlight.

Dr. McEwen thought Dr. Smith's paper was timely. In Chicago the material showing syphilitic lesions was greatly reduced, mouth lesions especially were becoming far less common. The mucous patch is seen today with nothing like former frequency.

He thought the percentage of extragenital chancres generally accepted was far too low and believed there should be a greater emphasis on the possibility of extragenital chancres in the consideration of syphilis.

He considered the solution of the problem raised by Dr. Smith to be in the use of models, and he would like to see moulages of skin diseases much more extensively used in teaching, not only the lesions of syphilis but also the primary and consecutive lesions of the skin with which the beginning student of dermatology must struggle.

Dr. Engmann thought one point should be emphasized in regard to the disappearing lesion. Certainly all had noticed that it was difficult to obtain proper material for teaching. It had occurred to him that a different strain of syphilis might be developing. It was a question whether this was due to the arsphenamin alone, or whether it had affected the chemical affinity of the spirochete. Every one knew that there was an enormously increased percentage of visceral and nerve syphilis, and while this might be due to a large extent to the improved methods of diagnosis, it had occurred to him that there might be a change in the chemical affinities of the organism.

Dr. Stokes believed it was possible to reconcile the views of Dr. Smith and Dr. Wile. The available material in acute and early syphilis depended on the source from which the clinic was drawing. When he went to Rochester he

saw practically no early syphilis; all the syphilis was late and of an unfavorable type for treatment. But of late he had seen more and more cases of early syphilis because many patients were becoming critical of the general practitioner's antiquated methods and traveled to the place where they had heard syphilis was being treated properly. This is a phase in the development of every clinic; the long-standing clinics which have been doing their teaching work among the profession effectively, eliminate the work that is coming to them. On the other hand, the newly established clinic that is doing good work draws early cases to it until its methods become common property. Both clinics are effective in different phases of the disease.

Dr. Stokes had tried experiments in giving photographic clinics. This was the only method available to him at first in teaching the large body of Fellows at the Mayo Clinic. He had become firmly convinced that it was not color which made the diagnosis of the lesion. If color photography sacrificed detail it should not be used, for it was the detail that did the teaching work. In looking at Dr. Wende's beautiful pictures he was at once impressed with their detail. He had tried the experiment of getting as much detail as possible in a photograph and then enlarging it. A man could be taught in this way to diagnose erythematous lupus, for example, from the photograph. When a case was later encountered in the clinic, he could at once pick it up.

Dr. Stokes believed Dr. Smith was right, that there would be progressively fewer visible lesions, and that students should be taught diagnosis by objective signs that do not depend on the mere visibility. They should acquire all of this knowledge possible against the day when there will be little early syphilis to see and teach from, but perhaps a great deal of late syphilis to cope with.

Dr. Schamberg could not bring himself to the belief that there had been any increase in visceral syphilis through the introduction of the newer methods of treatment of this disease. He thought there was an apparent increase, due to a more enthusiastic and careful search for these lesions.

Dr. Smith (closing) agreed with Dr. Schamberg that there was no increase in the number of visceral cases, except that they were checked up and recognized by the newer methods of diagnosis. The number of patients in his clinic was constantly increasing. The department was started in 1914 with thirty-five patients and now there was a maximum attendance of 160. Many of the patients have received one, two or three injections of arsphenamin outside, and then have heard, possibly, that they were not receiving just the line of treatment they should receive and come to the clinic. If these patients are examined they usually show serologic evidence and perhaps a certain amount of clinical evidence that they are syphilitics, and while they make up a large bulk of the work, they are practically worthless for teaching purposes.

Dr. Smith agreed with Dr. Grindon, who said that one unconsciously pictured to himself the proper color in the black and white photograph, which is practically impossible for the student who has no standard of color for the various skin eruptions. He considered the colored photographs of great assistance and hoped that through some sort of process it might be possible to reproduce colored prints that would be of more value than the ordinary black and white.

STREPTODERMATITIS, ESPECIALLY IN ITS RELATIONSHIP TO WOUNDS

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AND

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Streptodermatitis as a complication of wounds may give rise to a degree of misery and discomfort far surpassing its evident seriousness. The best general description of this form of dermatitis is that it resembles a superficial burn. The bright red patch may spread by a sharp margin, and so remind one of erysipelas, from which it differs in its superficiality. In other cases it may spread by dissecting along under the horny layer of the epidermis, causing a ragged undetermined border, or it may extend by minute, diffusely scattered red spots, which gradually coalesce with the main patch. The surface may be red and raw and may weep a clear serum like a recent burn; or it may be purulent and covered with crusts; or it may be finely vesicular or bullous, resembling a vesicular eczema. The latter phase may occur in eczematous patients, and is often designated acute vesicular eczema. In any form the itching and burning may be tormenting and may constitute a most serious embarrassment to the patient recovering from a wound.

The features of the disease demanding special consideration during treatment are:

First, streptodermatitis is an infective disease, and therefore requires the employment of antiseptics. Second, the septic agent, a streptococcus, is an anaerobe and therefore many forms of occlusive dressing are inadvisable as favoring its growth. Third, the skin is in a highly irritable condition, and all topical applications, which are at the same time irritating, must be prohibited. In fact, the antiseptics employed should be, as a rule, so dilute as to be nonirritating to the skin, and should be inhibitory rather than annihilating to the microorganisms.

SOLUTION OF LEAD SUBACETATE

For a long time dermatologists and surgeons employed this agent on wounds and on raw infected surfaces, supposing that it controlled inflammation by its styptic or astringent action on the tissues and blood vessels. The principle of oligodynamic action, first enunciated in a posthumous paper by Naegeli in 1893, may afford an explanation.

OLIGODYNAMIC ACTION

The epithet oligodynamic [1] is given to the poisonous action of minute traces of certain metals in water, such as copper or lead. The metals in question are present either as the hydroxid or carbonate in the colloidal state. Historically, it is highly interesting that it is these two metals, the acetate of lead as Goulard's extract and the sulphate of copper, or eau d'Alibour, which have been used for so long, and in a very dilute solution, as tropical remedial agents for external inflammatory conditions. We shall consider the probable mode of action of lead.

Acetate of lead in the presence of a fluid, such as serum rich in carbon dioxid, would form carbonate of lead, a particularly bland form of this bland and unctious metal. This change of the acetate into the carbonate is so inevitable and so easy that it constitutes the commercial way of making white lead. In this process, lead buckles are placed in jars of vinegar, thus forming the acetate, and these jars are exposed to the carbon dioxid gas emanating from the fermentation of tan bark. At ordinary temperatures the carbon dioxid is the stronger radical and displaces the acetate, thus forming the carbonate. Similarly, the acetate of lead in a lotion would turn into the carbonate by coming into contact with the carbon dioxid in a serum oozing from a pathologic lesion. Furthermore, the carbonate would precipitate in very fine division and in a medium admirably adapted to its becoming colloidal.

Copper seems to be the most powerful of these oligodynamic metals. Naegeli estimated the amount of copper present in 12 liters of distilled water, which had been four days in contact with twelve two-pfennig pieces, as being one part in seventy-seven million, yet it was powerfully toxic to Spirogyra, killing it in one minute. Copper lotion as eau d'Alibour has always been a favorite in France, but has never become so either in England, Germany or America. On the other hand, lead lotion, in spite of profound changes in surgical technic, has never been displaced entirely in any of the latter countries.

Solution of lead subacetate consists of lead acetate 180, lead oxid 110 and distilled water to make 1,000. A mistake frequently made is to employ it too strong. A teaspoonful to a pint of distilled water is quite strong enough; we usually use it in one fifth of this strength. So diluted and employed soaked in a compress, and covered with oil silk or rubber tissue, it does not interfere with the penetration of the

1. Bayliss, William M.: Principles of General Physiology, 1915, pp. 108 and 222.

water into the epithelial tissues, nor with the natural exfoliative processes of the epidermis, which are such a great aid in carrying off superficial bacterial invaders.

If itching is a feature, and it often is, a coal tar can be added to the lead. Hutchinson's lotion acts admirably in such a case:

℞ Solution of lead subacetate..... ℥ss
Solution of carbon detergent..... ʒiiss
Sig.: Hutchinson's lotion. A teaspoonful in a pint of warm water to use as a lotion.

This may be further diluted by employing two pints of water instead of one. The fact that the lead water, added to the tar liquor, is an incompatible mixture, forming a dirty greenish gray precipitate, does not appear to interfere with its efficacy. Such a mixture may be applied for hours with the greatest benefit.

A boric acid solution, made by adding one or two tablespoonfuls of boric acid powder to a gallon of hot water, also makes an admirable lotion. The boric acid acts as a mild antiseptic and also renders the water bland and isotonic. The addition of 10 per cent. of liquor alumini acetici to this is excellent. Aluminum acetate is a mild and efficient antiseptic, and it acts better in a dilute solution than in a strong one.

Silver, as well as lead and copper, has also an oligodynamic action, and has long enjoyed a reputation in this kind of dermatitis. Gougerot[2] advises its use in a 10 per cent. solution, applied once or twice a week. I think a better effect is obtained from the use of a much more dilute solution applied for a longer time, though not necessarily at shorter intervals.

Nitrate of silver solution is excellent for injection into fistulas and suppurating cavities, which may act as the focal origin of the dermatitis.

When it is desired to change a wet dressing for something else because of its being damp and soggy, a drying lotion containing a great deal of powder, or a paste containing a great deal of powder mixed with a fat such as petrolatum may be prescribed. An ointment should not be employed because it is too occlusive. The powdery lotions referred to above and pastes soak up the discharges instead of damming them back as an ointment would, and they allow the escape of heat, and do not absolutely preclude the air, an important point when dealing with anaerobic bacteria. An indifferent powder such as starch, zinc oxid, or talcum or a combination of them may be used with the addition of 1 to 2 per cent. of salicylic acid. Care should be

2. Gougerot, H.: La Dermatologia en Clientele, 1917, p. 398.

used in employing boric acid, as even when finely powdered, there are broken crystals in it which irritate the tender skin like particles of glass. In solutions these crystals are destroyed, and when boric acid is incorporated, whether in a paste or in an ointment, care should be taken, for the same reason, to melt it first, either with glycerin or fat.

Very often the crusting is a serious matter in this form of dermatitis. The formation of crusts may be regarded as a defensive measure on the part of the micro-organisms, as being anaerobic they pullulate better on the exclusion of air. It is necessary to remove the crusts without undue violence. A preliminary soaking with the above mentioned lead or boric acid lotions often answers well.

A boric acid starch poultice is often excellent for removing the crusts and for relieving congestion. It is made by adding a heaping tablespoonful of finely powdered common laundry starch to two tablespoonfuls of cold water, and then adding to this a coffee cup full of boiling water, stirring rapidly until the mixture forms a thick paste. To this paste should be added a tablespoonful of boric acid powder, stirring until it is dissolved. Starches differ a little in their paste-forming quantities, some requiring a little more and some a little less of the starch powder to form a paste of the proper consistency for a poultice.

CLEANING THE SURFACE

Cleaning the surface of the highly irritable skin from its débris of cells, fat, pathologic secretions, crusts and dried on, precipitated applications is an important matter. Plain water is even more unsuitable than on the normal skin, as the oily surface sheds it and it is hypotonic. The addition of soap, as in our daily ablutions, makes the water still more irritating. The addition of boric acid improves it, but it is not sufficiently detergent. Alcohol, so admirable in many situations, is too sharp. Benzin or gasoline is excellent, as they are wonderfully solvent for both fats and crusts and rarely irritate.

Under a well directed treatment, streptodermatitis disappears in from six to eight weeks or sooner, except when complicated by eczema, when the duration of the malady may extend into years.

The important matters to remember are that this dermatitis is an infective disease demanding the employment of antiseptics which must be mild and must be used very dilute. Occlusive dressings are not to be employed. Moist dressings, as indicated, and pastes, in which the amount of powder in the fatty base is great (50:50), are not occlusive in the sense meant. In cleaning the affected surfaces, only mild measures are permissible.

Streptodermatitis may arise from a chafing or from a slight abrasion which, by the time the disease is in full swing, has disappeared. Sometimes, however, its seat of origin is clearly in evidence, as in a suppurating wound or at the mouth of a fistula leading, for example, from an osteomyelitis. It may arise long after the wound—the site of its origin—has healed, as in a case which came under our observation a short time ago. The original patch having started, it may be transferred by the hands, especially by the nails, to different parts of the cutaneous surface. It may spread over the entire cutaneous surface, including the face, scalp, palms, and soles, and so give rise to a kind of dermatitis exfoliativa. The misery of the patient can then be said to be complete.

News and Comment

SPIROCIDE (MERCUPRESSON)

Several physicians have written to the ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY concerning a circular that they have received extolling the virtues of "spirocide (mercupresson)," in the treatment of syphilis. Accompanying the commercial circular is a reprint by Dr. J. Lewengood reporting the results, surprising to him, which he has obtained in certain cases of syphilis by using this remedy. On examination it proves to be a combination for administering fumigations. In addition to mercury, it contains certain vegetable substances and copper. The use of vegetable substances—"alteratives"—for the efficient treatment of syphilis belongs to past days. In this preparation they are burned up anyway. If the copper were volatilized at all, it would be of no known virtue in syphilis. The treatment, therefore, reduces itself to a method of mercurial fumigation. The treatment of syphilis by fumigation can, of course, be used effectively. It was used in the dawn of the history of syphilis, but it has not maintained its position, chiefly, doubtless, because it is inexact and dangerous. As a new means of treating syphilis spirocide is about in the class that the sixteenth century blunderbuss is among firearms. Neither the commercial claims nor the so-called scientific claims which it furnishes are entitled to serious consideration.

It is depressing that efforts to exploit us with things of this sort are constantly recurring, and it is deplorable that endorsements of such remedies are given on the basis of uncontrolled experiments by captains, majors, colonels, state public health officials and other medical men who should be careful of what they endorse. Experience is fallacious, and judgment difficult, particularly with remedies for syphilis.

THE DEATH OF DR. ISADORE DYER

Dr. Isadore Dyer, dean, and professor of diseases of the skin, Tulane University of Louisiana School of Medicine, New Orleans, died on October 12, 1920. An obituary will appear next month.

Abstracts from Current Literature

RELATION PATHOGENIQUE ENTRE LES LEUCEMIES ET CERTAINES DERMOPATHIES (THE PATHOGENIC RELATION BETWEEN THE LEUKEMIAS AND CERTAIN DERMATOSES).

L. M. BÉTANCÈS, Haematologica **1**:1 (April) 1920.

Mr. Bétancès has written a very interesting and complete monograph on the subject of the etiology and pathogenesis of the cutaneous manifestations of leukemia. In the first place he believes that the theories concerning the hemopoietic organs and their function are erroneous. After numerous histologic examinations of the lymphatic glands and spleen and of the cutaneous lesions in cases of leukemia, he has been able to prove that all the symptomatic complexes known under such names as dermatitis exfoliativa (Wilson-Brocq), pityriasis rubra (Hebra), dermatitis polymorpha (Brocq), dermatitis premycotica, lymphosarcomatosis (Sternberg), chloroma, myelomatosis (Kahler), adenia (Trousseau), Hodgkin's disease, mycosis fungoides, lymphadermia (Kaposi), lymphogranulomatosis (Paltauf-Sternberg), leukanemia and leukosarcomatosis are due to disturbances of hemopoiesis. According to him, Ehrlich's hemopoietic dualism is a false conception. He thinks that instead of two different hemopoietic tissues, that of the marrow of the bones and that of the lymphatic glands and the spleen, producing respectively, the myeloid and the lymphoid cells, there is only one which may produce, as required, myeloid or lymphoid cells. This hemopoietic tissue is situated in the bone marrow, the lymphatic glands, the spleen, and also in a latent state in the connective tissue of the body. He quotes: "The specific hemopoietic tissue (hemocytoblastic) and the diffuse hemopoietic tissue (hemohistoblastic) are embryologically and physiologically identical; thus they form a single anatomic system which may be termed the hemopoietic parenchyma or unity." (Ferrata and Negreiros, Rinaldi, A. Ferrata.)

After a short review of the pathogenesis of the leukemias, which he considers a hyperplasia of the hemopoietic parenchyma, Bétancès refers to the histologic changes in the lymphatic glands, bone marrow, spleen, liver, kidneys, tonsils, lymphoid nodules of the intestines, blood vessels and skin. The cutaneous lesions may be generalized or localized. The skin is thick, swollen, sometimes red and oozing and sometimes reddish yellow or gray and dry. The epidermis is covered with scales of variable size, rather thin and dry; the hair and nails show dystrophic changes and may disappear entirely. Occasionally the erythroderma remains localized and there is the formation of bullous lesions, psoriatic plaques or eczema (polymorphous erythema). Sometimes there are nodules and tumors, which may ulcerate. Microscopically there are, in the papillary region and in the corium, numerous lymphoid cells, hemocytoblasts, lymphoblasts and Ferrata's monoblasts. The connective tissue forms a sort of wide meshed reticulum filled with these cells, which occasionally form masses around the blood vessels. Mast cells and plasma cells, eosinophils, neutrophils, and some peculiar blood cells like those described by Turk and Rieder are abundant in certain cases. The changes in the epidermis are those of atrophy and dyskeratosis.

The author's conclusions are:

1. Dermatitis exfoliativa (Wilson-Brocq), pityriasis rubra (Hebra), dermatitis exfoliativa (Vidal-Leloir), polymorphous dermatitis (Brocq), dermatitis premycotica, lymphosarcomatosis (Sternberg), chloroma, myelomatosis (Kahler), adenia (Trousseau), Hodgkin's disease, mycosis fungoides, lymphadermia (Kaposi), lymphogranulomatosis (Paltauf-Sternberg), leukanemia, leukosarcomatosis and all other forms of leukemia, are diseases of the hematopoietic system.

2. The pathogenic process in all these diseases is exactly the same. It consists of a hyperplasia of the hemopoietic histologic unity, with a total or partial incapacity of the same to form differentiated myeloid or lymphoid cells.

3. This process is caused by certain lymphotoxins, myelotoxins or toxic lipoids acting on the hemopoietic unity and producing an exacerbation of its function.

PARDO-CASTELLO, Havana.

EXPERIMENTAL PELLAGRA IN WHITE MALE CONVICTS. JOSEPH GOLDENBERGER AND G. A. WHEELER, Arch. Int. Med. **25**:45 (May) 1920.

This work was carried out at the Rankin farm of the Mississippi penitentiary on eleven convicts who volunteered for the test. Those chosen had no previous history of pellagra either in themselves or in their families. The volunteers were placed on shorter work hours and had regular rest periods, their work being in the fields and classed as moderate or light.

The observations extended from February to October. There was no change in food until April 19, but the diet was restricted after that date. The average intake of each patient varied from 2,500 to 3,500 calories, 41 to 54 gm. of protein, 91 to 134 gm. of fat and 387 to 513 gm. of carbohydrate. The diet consisted of highly milled wheat flour, maize meal and grits, cornstarch, white rice, cane sugar, cane syrup, sweet potatoes, pork fat, cabbage, collards, turnips, turnip greens, coffee, "Royal" baking powder, salt and pepper.

None of the control patients developed pellagra, although in contact with it, while six of the eleven experimental patients developed evidence of this disease, the first symptoms appearing during the second month of the test diet. These symptoms were weakness, abdominal discomfort and headache; loss of weight became marked in the last few weeks of the experiment.

Six of the eleven developed skin lesions, beginning about five months after the institution of the diet, the first lesions beginning on the scrotum; later lesions appeared on the hands in one case and on the neck in another.

The authors consider that these six patients developed pellagra as a result of the experimental diet and they emphasize the early development of the scrotal lesion which appears to be much more common as an early symptom than has been previously recognized. They state that there may be certain qualities in diets which determine the initial dermatitis of an attack, these differences in quality corresponding to certain differences in clinical types.

They further state that the "dietary factors to be considered as possibly essential are (1) amino-acid deficiency, (2) faulty mineral supply, and perhaps (3) an as yet unknown (vitamin) factor."

JAMIESON, Detroit.

DIE ENTWICKLUNG UND DER HEUTIGE STAND DER ROENTGEN-BEHANDLUNG DES FRAUENBARTES (THE DEVELOPMENT AND PRESENT STATUS OF ROENTGENOTHERAPY OF FACIAL HYPERTRICHOSIS IN WOMEN). FRITZ M. MEYER, Dermat. Ztschr. **29**:334 (June) 1920.

The history of the roentgen-ray treatment of hypertrichosis is given, with an outline of the writer's experiments in this field. The present method is to divide the face into six or eight parts, when one is dealing with a universal hyperthricosis, and to ray each area for three "Volldosen" (510 F., according to Fürstenau) through 4 mm. of aluminum. After fourteen days the hairs begin to fall out, and after twenty-five days the epilation is usually complete. It is necessary, six weeks after the first radiation, to repeat the treatment, and a third application of an equal dose is given eight weeks after the second. The three sessions are necessary for success in favorable cases (those in which all the hair falls out after the second exposure). In general, one or two more rayings are given, at ten week intervals after the third. These later exposures may be one-sixth smaller than the early ones. Black, long hairs are most favorably influenced; long thin down is less favorable, and light small down growths are very refractory. The hairs of the upper lip fall with difficulty and return easily. In otherwise successful cases, the upper lip may have to be given individual raying.

The skin and mucous surfaces of the face are swollen after the exposures, and there is a drying of the mouth, with loss of salivary flow and diminished appetite. If the exposures are repeated too rapidly, headache, neuralgia, indisposition and lassitude may follow and persist for from twenty-four to forty-eight hours. The gums are protected by rubber infiltrated with lead, and pains which were frequent before this refinement of technic was introduced have not been complained of since. No permanent injury has been done.

GOODMAN, New York.

LA PONCTION LOMBAIRE DANS L'INTOXICATION PAR L'OXYDE DE CARBONE (LUMBAR PUNCTURE IN CARBON MONOXID POISONING). LEGRY and J. LERMOYEZ, Bull. de l'Acad. de méd. **84**: 67 (July 27) 1920.

In carbon monoxid poisoning the reaction must be thought of more as a corticopial congestive and hemorrhagic process which the intoxication produces than as an intoxication. In a recent case, the writers on their first lumbar puncture found a spinal fluid which appeared like almost pure blood. Such evidence of a hemorrhagic state is not constant in all cases. Lesieur and Rebattu have reported cases with spinal fluid free of all anomaly. Though the patient whose case is cited showed a bloody spinal fluid and serious symptoms, his wife and daughter presented only transitory malaise though subjected to precisely the same exposure to the gas. To explain this peculiarity, the authors mention the writings of Balthazard and Nicloux and of Bollet. While in normal persons the coefficient of intoxication is very constant, it is noticeably lowered in the person with a coexisting defect, such as chronic nephritis or hepatic cirrhosis. Other similar visceral alterations can assuredly lower resistance. Regarding their own case, they conclude that the patient's point of weakness lay in the nervous system itself. In the war he had had

cerebrospinal meningitis and twice had suffered concussion with loss of consciousness. Such antecedent occurrences are enough to create a special vulnerability to the gas in spite of the small amount inhaled.

It is suggested that chemical examination of the spinal fluid offers a means of diagnosis in uncertain cases.

DAVIS, New York.

KLINISCHE UND HISTOLOGISCHE BEOBACHTUNGEN AN TAETOWIERTEN (CLINICAL AND HISTOLOGIC OBSERVATIONS OF TATTOO MARKS). E. ARNING, Arch. f. Dermat. u. Syph. **123**:225, 1916.

Tattooing is universal among sailors. Only the South Sea Islanders mark the face. The most beautiful work is done by the Japanese. Prostitutes and criminals also have much tattoo. The Japanese use India ink for blue-gray, cinnabar for red, indigo and curcuma for green, and curcuma alone for yellow. European tattoo workers use India ink, carbon, cinnabar and occasionally carmin. Arning had the opportunity of studying several cases in which the use of cinnabar for tattooing resulted in a local reaction which clinically closely simulated tuberculosis verrucosa cutis, and indeed several dermatologists made that diagnosis, considering that the organism of Koch was introduced with the sputum used to mix the tints. It was easily disproved, however, because only the red gave the reaction, and all of the tints were mixed with the same sputum. Arning considered that he had to deal with an idiosyncrasy to mercury, which he demonstrated by applying a square of mercurial plaster to the patient's arm, with a resulting local reaction. He pictures a moulage of cinnabar dermatitis and the reaction to mercury plaster.

Arning also observed a patient with secondary syphilis, in whom the red areas of his tattoo (mercury sulfid) were free of lesions. Dohi first called attention to this relative immunity in 1909, since which time Florange, Holland and others have reported cases. Arning does not believe it is the result of any spirocheticidal effects of the mercury salt deposited in the skin, but of the local infiltration reaction to the foreign body. He is still working on this phase of the problem.

GOODMAN, New York.

EPITHELIOMATOUS ULCERATION AMONG TAR WORKERS. W. J. O'DONOVAN, Brit. J. Dermat. **32**:215 (July) 1920.

O'Donovan states that the increasing importance which is being attached to the industrial etiology of disease is reflected in the increasing number of occupational diseases that are being made notifiable. Epitheliomatous ulceration due to tar, pitch, bitumen, mineral oil or paraffin, or any compound, product or residue of any of these substances, and chrome ulceration are the latest diseases made reportable.

The author cites the widespread and increasing use of these substances in present day industry, and gives figures showing the frequency of occurrence of warts and epitheliomas among workers. A review of the literature shows that Volkmann in 1875 was probably the first to call attention to a definite industrial tar etiology of malignant disease.

In considering the clinical aspects of the subject O'Donovan cites a number of cases, and finds the following outstanding points in regard to tar epitheliomas:

(1) There is a variation in age among those affected with carcinomatous lesions.

(2) Long duration of employment is common before the development of serious lesions.

(3) Many growths that have needed operative treatment have a short history.

(4) In a few cases single lesions of long duration have needed operative relief in the end.

(5) Although tar warts may have existed for years, even twenty-five, the change in type and rapid growth of a new lesion causes the worker to seek early surgical advice.

The prognosis in these cases is good, and papillomas, in all respects similar to other tumors removed and proved microscopically to be carcinomatous, have generally fallen away after from two to four months duration. Treatment is surgical, though there is no objection in the case of new lesions to deferring operation for a few months to see if a natural cure is probable by dehiscence.

SENEAR, Chicago.

TUMORS OF THE BLADDER, INCLUDING REPORT OF VEGETATING SYPHILOMA OF THE BLADDER. W. C. DANFORTH and B. C. CORBUS, Surg., Gynec. & Obst. **31**:219 (Sept.) 1920.

During seven months, seven cases of bladder tumors have been observed. One patient presented condyloma which closely simulated a true tumor growth. This woman was 25. She complained of pain over the lower abdomen, painful and frequent urination, and loss of weight. A Wassermann test, made three days after admission, was slightly positive; a second test two days later was negative. Cystoscopy showed the entire bladder floor occupied by an infiltrating growth with many peaked projections of papillomatous character, together with larger, rounded masses, the upper portions of which showed a translucency indicating edema. A small piece of tissue was secured by cystotomy and examined. The pathologist reported that, while the specimen had been somewhat injured by drying, none of the sections showed malignancy but merely appeared to be necrotic material. The patient was given nine intravenous arsphenamin injections. She immediately began to improve and cystoscopy disclosed a marked regression of the growth at the base of the bladder, the distinguishing characteristics of which, however, were still plainly visible.

(Dr. Leo L. Michel has called my attention to two plates in "Traité pratique de cystoscopie" by Marion, Heitz-Boyer and Germain [Masson et Cie, 1914], entitled "Bullous edema on lateral face of bladder," and "Bullous edema of a particular form situated on the upper part of bladder," which closely resemble the figures pictured in the article of Danforth and Corbus.)

GOODMAN, New York.

UEBER DEN VERLAUF DER AUF DEN MENSCHEN UEBERTRAGENEN TIERSYPHILIS (PROGRESS OF HUMAN SYPHILIS ACQUIRED THROUGH ANIMALS). A. BUSCHKE, Arch. f. Dermat. u. Syph. **123**:278, 1916.

Buschke reported in 1913 the case of a laboratory assistant who acquired syphilis from a rabbit. The subsequent history of this patient is presented. Buschke is led to believe that the virus was not reduced in virulence for man

by passage through at least six or seven rabbits. There are two other incidences in the literature of syphilis transferred back to man from rabbits. In neither case is there reason to believe that the disease ran a milder course than human to human infection. In one of these cases, there had been sixteen rabbit passages of the infectious material. Metchnikoff reported two cases of syphilis transferred back to humans from apes. In both these the disease is supposed to have run an exceedingly mild course.

GOODMAN, New York.

UEBER QUECKSILBERINJEKTIONEN BEI KINDERN UND SAEUGLINGEN (MERCURY INJECTIONS IN CHILDREN AND INFANTS). JOHAN ALMKVIST, Arch. f. Derm. u. Syph. **121**:895, 1916.

Mercury may be given to nurslings and young children with good clinical results in syphilis. Children under 1 year, for example, may receive 2 mg. per kilo of weight every third day for a course of ten injections. Increase in weight is a guide to the condition of the patient.

GOODMAN, New York.

INDUSTRIAL DERMATOSES, THEIR SOURCES, TYPES AND CONTROL. W. A. PUSEY, Proc. National Safety Council, 1919, p. 632.

In this paper, read before the health section of the National Safety Council, Pusey reviews in a general way the subject of industrial dermatoses, discussing the rôle played in their production by (1) heat, (2) cold, (3) weather, (4) posture, friction, pressure, (5) parasites, (6) infections, and (7) mechanical and chemical irritants. He calls attention to the extent and importance of the problem of industrial dermatoses, neglected because the experts in industrial medicine are not trained in dermatology, and recommends that one way of undertaking systematic investigation would be to employ a few trained dermatologists to devote all their time to an investigation of industrial dermatoses. These could be younger men and there could be associated with them a consulting board of mature experts in skin diseases.

SENEAR, Chicago.

SYPHILOMA VULVAE. ARTHUR STEIN, Surg., Gynec. & Obst. **31**:227 (Sept.) 1920.

The descriptive term syphiloma vulvae is applied to the disease formerly named "esthiomene." Histologically, the hypertrophied masses of the diseased area are gummatous and subject to the familiar necrotic changes and cicatricial contractions seen in gummas. Clinically, the vulvar changes become manifest a long period, sometimes many years, after the primary infection. Syphilitic induration of the vulva is apt to supervene in the absence of all other specific changes after a long interval of apparent health, which accounts in part for the many mistakes in diagnosis. The treatment is both surgical and medical. Operative interference consists of excision and destructive cauterization of all tumors and excrescences. Arsphenamin intravenously is an essential supplement to the surgical treatment. Stein observed two cases at the Harlem Hospital, both in colored patients. He gives photographs of the clinical cases, and photomicrographs, also a bibliography.

GOODMAN, New York.

LEIOMYOMA. L. Savatard, Brit. J. Dermat. **32**:229 (July) 1920.

Savatard described a typical case of this rare condition. The patient, a man, aged 48, presented over the right malar region and on the external aspect of the right forearm numerous discrete nodules, varying in size from a pin head to a small berry. They varied in color from yellowish brown on the cheek and dull red on the arm, and disappeared on pressure. The nodules were firm, though of varying induration, and were movable with the skin. Some of the larger ones were very sensitive to pressure and to changes of atmosphere and temperature. Excruciating pain followed gentle manipulation of one of the larger tumors. Pain was also induced by wet weather and when the patient left a warm room. Radium and roentgen-ray therapy were without effect except that no pain had been felt in the facial lesions since the application of radium.

The microscopic picture disclosed a tumor composed entirely of smooth muscle cells. There were fine interlacing bundles of collaginous fibers in the tumor proper which gradually increased in size toward the periphery of the growth, but there was no suggestion of a fibrous capsule. No sebaceous and sweat glands or nerve filaments could be detected, but there was a hair follicle near the center of the growth. Savatard states that in his case the origin was clearly from the arrector pili.

Senear, Chicago.

DREI JAHRE AMTLICHER SYPHILISTILGUNG MIT SALVARSAN (THREE YEARS OF AN OFFICIAL CAMPAIGN AGAINST SYPHILIS BY USE OF ARSPHENAMIN). Victor L. Neumayer and Marianne Neumayer, Arch. f. Derm. u. Syph. **121**:820, 1916.

Rendering active syphilitics noninfectious with arsphenamin or its equivalents has markedly reduced the incidence of infection in the district of Bosnia. The mixed population of Christians and Mussulmen presented a special problem in that the Mohammedan women were at first not examined because of the religious interdiction. As a consequence the syphilitic infection reappeared in the younger children, and indeed was carried from one woman to another through the communal smoking custom. The men were, of course, infected through the women of their own household. It is interesting to note that the authors report but one case of tabes and no case of paresis in eight years' observation in this district.

Goodman, New York.

BEOBACHTUNGEN UEBER DIE URSACHEN DER VERSCHIEDENEN LOKALISATION DER SYPHILITISCHEN EXANTHEME (CAUSES OF VARIATIONS IN THE LOCALIZATION OF SYPHILITIC EXANTHEMS). John Almkvist, Arch. f. Dermat. u. Syph. **123**:207, 1916.

Passive hyperemia renders a part of the body more or less susceptible to the syphilitic virus. Active hyperemia or anemia acts against the development of syphilitic changes of a portion of the body. It would appear that the relative susceptibility of the organs, not only the skin, depends in some measure on its blood distribution, in the sense of active or passive hyperemia, or anemia. It is also possible that the prognosis of a developing syphilis depends to a great measure on the state of blood distribution during the secondary stage of the disease. Other factors may of course be operative.

Goodman, New York.

RECKLINGHAUSEN'S DISEASE WITH SURGICAL COMPLICATIONS. C. E. CALDWELL, Surg., Gynec. & Obst. **31**:242 (Sept.) 1920.

The conditions, fibroma molluscum, neurofibroma, and plexiform neuroma are included under the title of von Recklinghausen's disease. It is not unreasonable to assume that these conditions are dependent on some constitutional vice, probably some abnormality of the endocrine glands. Stein reports two of his cases which had complications of a surgical nature: fibroma of the ulnar nerve, degenerative changes in a large neurofibromatous mass, with accompanying neurovascular changes.

GOODMAN, New York.

CASE OF PURPURA WITH SYMMETRICAL GANGRENE OF THE FINGERS. MAY MICHAEL, Am. J. Dis. Child. **20**:124 (Aug.) 1920.

The author reports the interesting case of a child, 2½ years old, who was taken ill with fever, restlessness, and swelling of the glands of the neck. A slight cough and sore throat were also present. During the first week of the attack large purpuric patches appeared on both upper and lower extremities; the temperature was 103.5 F. A remission occurred, during which the child seemed fairly well. During a second attack of purpura the eruption covered the trunk and extremities; this lasted six weeks. After another remission of two weeks, the first phalanges of all the fingers of the right hand, and of the thumb, index, middle and little fingers of the left hand, began to look dry and gradually turned black. After a month in the hospital, the child rapidly improved, and the purpura disappeared. The first and second phalanx of the first finger of the right hand, and the first phalanges of all the other fingers, except the thumb and left fourth finger, dropped off, but healed smoothly.

The Wassermann test was negative, and blood cultures on several occasions failed to disclose any organism. The coagulation time of the blood was normal; urine, stools and tuberculin tests were negative.

The author concluded that an infectious obliterating endarteritis—the infection being the same as that which caused the purpura—was responsible for the gangrene.

OLIVER, Chicago.

ACNE ZOSTERFORMIS. A. BLASCHKO, Arch. f. Dermat. u. Syph. **123**: 242, 1916.

All linear dermatoses, or those that apparently follow the course of a cutaneous nerve, are not the result of local nerve disease. One must consider also anomalies of development, particularly in regard to segmental changes which result in a "locus minoris resistentiae." As a case in point, Blaschko reports the case of an 18 year old boy, in whom a general examination disclosed along the course of the seventh dorsal nerve left of the spinal column an area about palm sized, with numerous, thickly aggregated, black-headed comedones. A smaller group was situated in the mammary line of the same nerve, and still two smaller groups of three or four comedones at the lateral and midlines. No other comedones were in the area immediately adjoining. The case reminded Blaschko of nevus acneiformis, but the history disclosed that the patient had recently recovered from an attack of true zona and that the comedones first appeared after the regression of that disease. Apparently, some structural changes had occurred that were favorable to the development of comedones.

GOODMAN, New York.

USE OF QUARTZ LIGHT IN DERMATOLOGY. E. L. OLIVER, Boston M. & S. J. **183**:155 (Aug. 5) 1920.

This article gives a short history of the development of the quartz light and a discussion of its physics. The author states that the effect produced by sunlight and this light are identical; that the efficiency of treatment with the light is dependent on the dosage, and that most of the unfavorable results in certain types of cases are due to insufficient treatment. Comparatively little discomfort is produced by the erythema or by the blister if the Kromayer lamp is used.

In twenty-five cases of varicose ulcer, almost without exception improvement was more rapid than would be expected from other methods of treatment. The light treatment has given results more rapidly, has relieved the pain, has kept the patient on his feet, and the new epithelium has been thicker and firmer, and more nearly like normal skin. Exposures to the Alpine sun lamp, usually about two minutes at a distance of 10 inches, have been sufficient to produce a distinct erythema of the skin about the ulcer. The treatment was repeated every week and the time of exposure increased gradually.

Flat vascular nevi have also been successfully treated by pressure with the Kromayer lamp. Fifty per cent. improvement after a single treatment is not unusual. The amount of fading of these lesions on pressure is a valuable measure in evaluating the result. Incidentally the author gives a word of warning against the too free use of radium in portwine marks because of subsequent changes in the skin. Alopecia areata often responds very favorably. In other types of alopecia its use is doubtful. In chronic patches of psoriasis, especially of the nails, in resistant patches of chronic eczema, and in a few cases of pruritus ani and pustular acne vulgaris it proved of value. Its availability, time saving, and ease of application are emphasized as advantages of the quartz light over natural sunlight.

LANE, Boston.

[NOTE.—Of course, many other competent workers have failed to get such favorable results with the Kromayer lamp, notably in nevus.—ED.]

EIN BEITRAG ZUM KAPITEL: DERMATOLOGISCHE KRIEGSERFAHRUNGEN (WAR EXPERIENCE IN DERMATOLOGY). J. F. VON CRIPPA, Arch. f. Dermat. u. Syph. **123**:285, 1916.

Self inflicted dermatologic lesions were not unknown among the German forces. The means employed and diseases simulated were those of other countries. Natural skin diseases were made worse or healing disturbed. It is interesting to note that Crippa is certain that the German troops were less subject to these practices than those of their opponents, for example, the English. [On the other hand, Davis (Dermatitis Artefacta in the Army, *Arch. Dermat. & Syph.* **2**:82, 1920) says that there were few cases in the British Forces.]

GOODMAN, New York.

ACTINOMYCOSIS OF THE LOWER LIP. JOHN R. HARGER, Surg., Gynec. & Obst. **31**:305 (Sept.) 1920.

Harger presented a case before the Chicago Surgical Society. Microscopic section disclosed the ray fungus.

GOODMAN, New York.

NOCHMALS ZUR KLINIK UND ZUR STELLUNG DES "BENIGEN MILIARLUPOIDS" (CLINICAL STUDY AND CLASSIFICATION OF BENIGN MILIARY LUPOID). C. Boeck, Arch. f. Derm. u. Syph. **121**:707, 1916.

Multiple benign sarcoid is clinically and histologically a constitutional bacillary infection, which is probably a distinct but mild type of tuberculosis. The excitant of the disease, which tinctorially and morphologically is indistinguishable from the bacillus of Koch, is demonstrable in the sections of the vegetating but not the ulcerating mucosa of the nasal passages. Inoculation of guinea-pigs has given characteristic results.

Goodman, New York.

ARSPHENAMIN AND NEO-ARSPHENAMIN. W. A. Smith, J. Lab. & Clin. M. **5**:518 (May) 1920.

Smith gives a brief résumé of the origin, present supply and rules for manufacture of these therapeutic agents. In the technic of administering the drugs, nothing new of importance is mentioned. Reactions and their causes, also the use of the preparations in treatment are discussed, and a number of references to the literature are added. In his discussion of the comparative value of the two preparations, the author quotes freely from Schamberg's recent articles showing that neo-arsphenamin is two and one-half times less toxic for white rats than the arsphenamin from which it is made. Arsphenamin was tolerated at 100 mg. per kilogram of body weight, while the neo-arsphenamin was tolerated at 250 to 300 mg. per kilogram. Arsphenamin in practically all concentrations hemolyzes red blood cells in vitro; neo-arsphenamin does not do so in any concentration normally used.

Arsphenamin is more curative than the neo-arsphenamin. Schamberg found that to sterilize rats experimentally infected with *Trypanosome equiperdum* (horse syphilis) it took twice as much of neo-arsphenamin as of arsphenamin. The arsenic content of three parts of neo-arsphenamin equals that of only two parts of arsphenamin. Schamberg thus concludes that the arsphenamin is more active therapeutically, but this difference is made up by the discrepancy in tolerated dosage, as 0.9 gm. of neo-arsphenamin can be given three times a week. Neo-arsphenamin creates much less biochemic disturbance in the blood and tissues.

Waugh, Chicago.

TREATMENT OF ANGIOMAS WITH RADIUM. William S. Newcomet, Am. J. Roentgenology **7**:337, 1920.

In radium, as in the roentgen ray, we have an agent that is capable of doing considerable harm under some circumstances; therefore it must be employed with great care, especially when it is impossible to judge exact dosage. It should be remembered that as a rule people live in the present and to a great extent forget the past. Therefore, if a scar or slight discoloration remains, it may be judged a bad result with no regard for the former condition even if it should have been repulsive.

The amount usually given is about an erythema dose, which must be judged according to the applicator used, the filter and the skin distance. The last factor is by far the most important and varies according to the depth of

the nevus. If it is deep, the applicator is placed from 3 to 6 cm. away and moved frequently to produce "cross-fire" effect. The tubes are used exclusively. The skin bordering the nevus must be protected, and if filters are used, they should extend slightly over the edge of the nevus rather than expose the skin.

GOODMAN, New York.

GENERALISIERTE HAUTOEDEME BEI UNIVERSELEM EKZEM (GENERALIZED CUTANEOUS EDEMA IN UNIVERSAL ECZEMA). H. FUCHS, Arch. f. Derm. u. Syph. **121**:947, 1916.

A woman patient, aged 53, gave a history of having had a chronic eczema of the body for three years. The condition was relieved, and she was referred to the outpatient department. A universal edema set in, but the consistency was varied in different parts of the body. There was no evidence of heart or kidney disease. She rapidly gained 5 kg. despite treatment of all kind. She left the hospital at her own request. The follow up history stated that the edema had improved, but that the patient had lost weight and strength through a profuse diarrhea and had died. At no time during her illness was albumin detected in her urine. Fuchs believes that the eczema was the direct cause of the edema.

GOODMAN, New York.

LUES UND TUBERCULOSIS VERRUCOSA CUTIS (SYPHILIS AND TUBERCULOSIS VERRUCOSA CUTIS). H. FUCHS, Arch. f. Derm. u. Syph. **121**:955, 1916.

Three patients presented symptoms of their syphilitic infection which so closely resembled the picture of tuberculosis verrucosa cutis, that the diagnosis could not be made on clinical evidence alone.

GOODMAN, New York.

NOMA IN THE DOG. J. McJ. PHILLIPS and FRED BERRY, J. Infect. Dis. **27**:136 (Aug.) 1920.

A case is reported of a dog, 9 months of age, which after a mild attack of distemper, developed an ulcerative condition of the mouth similar in every respect to noma. Smears showed equal numbers of fusiform bacilli and spirilla. A majority of smears from the gums of a number of normal dogs in the same kennel contained B. fusiformis and spirilla, usually in small numbers. The occurrence in a dog of a noma so similar to that in man, makes it appear possible that the dog may be a source of infection to man, especially to persons recovering from acute diseases, who are more susceptible to such infection.

OLIVER, Chicago.

NAEVI ANAEMICI UND RECKLINGHAUSENSCHE KRANKHEIT (ANEMIC NEVUS AND RECKLINGHAUSEN'S DISEASE). O. NAEGELI, Arch. f. Derm. u. Syph. **121**:742, 1916.

Two patients presented a combination of von Rechlinghausen's disease and nevus anemicus. Probably more cases of this association have not been reported because the nevus has been mistaken for vitiligo.

HAUTALLERGIE BEI GONORRHOE. VERSUCHE MIT NEISSERSCHER GONOKOKKEN-BOUILLON (SKIN ALLERGY IN GONORRHEA. EXPERIMENTS WITH NEISSERIAN GONOCOCCUS BOUILLON). H. Fuchs, Arch. f. Dermat. u. Syph. **123**:331, 1916.

The intradermal injection of gonococcus bouillon excites in the majority of patients suffering with gonococcal infections a skin allergy that is not found in healthy persons. This allergy persists for several months after the disease has regressed, and does not depend on the clinical form of the disease. Ordinarily the phenomenon is first seen six days after infection. It is possible by means of this reaction to distinguish sequels that are dependent on the gonorrheal infection from those that are not.

VERTAEUSCHUNG EINES SYPHILITISCHEN PRIMAERAFFEKTES DURCH EINE NACH ORTHOFORMBEHANDLUNG EINER RHAGADE IM SULCUS CORONARIUS PENIS ENSTANDENE NEKROSE (NECROSIS AFTER ORTHOFORM TREATMENT OF RHAGADES OF THE CORONARY SULCUS OF THE PENIS SIMULATING PRIMARY CHANCRE). Otto Sachs, Wien. klin. Wchnschr. **33**:680, 1920.

A physician substituted orthoform for xeroform as a local application to coronal rhagades. The resulting clinical picture simulated a primary syphilitic lesion. Sachs reviews the use of orthoform and submits a bibliography.

DIE PIGMENTIERUNGEN DER HAUT BEI PERNIZIOESER ANAEMIE (CUTANEOUS PIGMENTATION IN PERNICIOUS ANEMIA). T. Schucany, Arch. f. Derm. u. Syph. **121**:746, 1916.

The study of the skin histologically of two cases of pernicious anemia and one of hemachromatosis, which clinically presented similar pigmentation, revealed a typical Addison pigmentation, a marked arsenmelanose, and an extensive deposition of hemosiderin. It appears that the skin changes in pernicious anemia are not of a single nature, and that for specific diagnosis, histologic examination of the skin is essential.

UEBER EINEN FALL VON PARAPSORIASIS (CASE OF PARAPSORIASIS). Muschter, Arch. f. Derm. u. Syph. **121**:918, 1916.

A case of parapsoriasis is reported which shows the three clinical types of the disease. This is the second case of the kind to be reported in the literature. The author is of the opinion that the three clinical types of the disease that have been described are not clinical entities but varieties of the same affection. He does not concur with Werther in naming the disease "pityriasis lichenoides chronica polymorpha."

ABNORMES HAARWACHSTUM NACH TIEFER TRICHOPHYTIE DES KOPFES (ABNORMAL GROWTH OF HAIR AFTER DEEP TRICHOPHYTOSIS CAPITIS). H. Fuchs, Arch. f. Derm. u. Syph. **121**:945, 1916.

Following roentgen-ray depilation and the use of mercury salve for tinea of the scalp, a boy of 9 years returned to the clinic presenting a most curious new growth of hair. Areas that formerly were diseased showed a heavier and darker growth than the former normal areas.

DER LICHEN SCLEROSIS (LICHEN SCLEROSUS). ARTHUR ALEXANDER, Arch. f. Derm. u. Syph. **121**:925, 1916.

Alexander describes two cases that are identical with lichen sclerosus (Hallopeau) yet whose lichen characters are so marked and distinguished that they clinically present no similarity to either scleroderma or white spot disease.

UEBER EINEN FALL VON HYPERKERATOTISCHEM EXANTHEM BEI GONORRHOE UND LUES (CASE OF HYPERKERATOSIS WITH GONORRHEA AND SYPHILIS). ERNST NATHAN, Arch. Derm. u. Syph. **121**:906, 1916.

A clinical and histologic presentation of this rare affection described for the first time in a patient with secondary syphilis and gonorrheal urethritis.

UEBER URTIKARIA UND URTIKARIELLE EXANTHEME (URTICARIA AND URTICARIAL EXANTHEMS). G. SCHERBER, Archiv f. Derm. u. Syph. **121**:765, 1916.

This article presents a critical review of the urticaria syndromes.

GOODMAN, New York.

Book Reviews

MANUAL OF TROPICAL MEDICINE. By ALDO CASTELLANI, C.M.G., M.D., M.R.C.P., Lecturer at the London School of Tropical Medicine, and ALBERT J. CHALMERS, M.D., F.R.C.S., D.P.H., Director, Wellcome Tropical Research Laboratory (Soudan Government). Third Edition. Pp. 2437. New York: William Wood & Co., 1919.

The third edition of Castellani and Chalmers' "Tropical Medicine" presents to us in enlarged form a work that is of the greatest value to dermatologists. It is valuable for its account of skin diseases in the tropics, but its greatest value lies in the systematic and exact exposition of the subject of the vegetable and animal parasites that attack the skin. In this field it is a reference book which the reviewer has in the past found invaluable. One cannot but admire to the highest degree the thoroughness with which these subjects have been covered.

Not less than 270 pages are devoted to the section on skin diseases, not including such important diseases as yaws, verruca peruana, leprosy and pellagra, which are treated under general diseases, nor the parasitology of skin diseases, which is a part of the general consideration of parasitology. This amount given to skin diseases is testimony to their importance in the tropics, and to the authors' familiarity with and interest in them. In the part devoted to skin diseases are considered not only many interesting infections unknown to us, but there are also descriptions of many familiar conditions in new guises as they appear in the tropics. Indeed, one is inclined to feel that many of the diseases which are described as new, or by new names, are familiar diseases intensified by tropical conditions. The only criticism which the dermatologist is likely to make of the book lies in this direction. There are undoubtedly many new names given to known affections. The authors apparently are rather ready to describe new conditions, especially those due to new species of vegetable parasites.

This new edition as a whole is a colossal work; it contains 2436 octavo pages and it is modestly called a manual! It ought to be in at least two volumes, for the single volume is unwieldy in size and weight, and cannot long hold together under much use. It is a veritable thesaurus of facts about the tropics and its diseases: The History of Tropical Medicine, Tropical Races, Tropical Climatology, Tropical Foods, Tropical Diseases, Fitness for Tropical Life—these are the chapter headings of the 127 pages of Part I, the introduction. Part II considers the Causation of Disease in the Tropics, and Part III, The Diseases of the Tropics. The whole of it is interesting reading.

The work is a monument to the industry, scientific zeal, and comprehensive scholarship of its authors. It is a great book.

SYPHILIS DE L'UTERUS ET DE SES ANNEXES (SYPHILIS OF THE UTERUS AND ADNEXA). E. OZENNE, Paris, Masson et Cie, 1920.

Ozenne has produced an excellent monograph on syphilis of the uterus and adnexa, including the mammary glands. The volume is worth a rapid perusal in order to glean the essentials of the contents, but it would be a worthy

addition to any library for reference, for it contains a wealth of detail, carefully assembled and clearly arranged. The bibliography is extensive, and the arrangement of the text is so simple and expository that it enhances the volume in the eyes of readers fancying the method of direction. The divisions of the book are: syphilis of the uterus, syphilis of the adnexa and syphilis of the breasts. Each division contains subsections devoted to the several stages of the disease, with a particularly valuable passage at the end of the first division on syphilis of the gravid uterus.

Some of the most striking points the author brings out are: In discussing the incidence of chancre of the cervix, he hints that it is found in this situation more frequently than elsewhere, but is not recognized partly because it resembles cancer, but more because by the time the patient presents herself the lesion is healed. When gravidae have primary syphilis the lesion is frequently found on the cervix, generally on the anterior lip.

There is a splendid description of the secondary and tertiary lesions of the cervix and of these phases of the disease in the uterine body, including both the symptoms and signs. Often gummas of the body of the uterus simulate in all clinical respects fibromyomas. There is an illuminating reference to the effect of syphilis on the gravid uterus, with particular consideration of dystocia due to primary cervical lesions, and the questions of the mechanism of miscarriage.

Syphilis of the tubes takes the form of salpingitis of different grades of severity, and gummas, according to the stage of the disease. Secondary ovaritis is likened to epididymitis, and gummas may develop with the symptoms of tumors or cysts. Mammary syphilis is reduced to a matter of recognizing primary and tertiary lesions, particularly the latter, because of their resemblance to tumors.

The book is undoubtedly a signal contribution to the clinical knowledge of syphilis. It is a pity that physicians have not the leisure to create a larger number of such monographs, for their place as reference sources cannot be exaggerated. Such works indicate a sort of scientific patriotism, for they represent untold drudgery, and are thus doubly to be commended.

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